The effects of acute stress on cognitive performance in older adults and patients with Parkinson's disease

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Abstract

Acute stress is a ubiquitous feature of everyday life, affecting young and old alike, and it has an important impact on cognitive well-being. However, stress research has largely been conducted in healthy, young adults, and important gaps remain in our understanding of the impact of stress on cognitive function of older adults. This thesis presents two studies that focus on separate populations: Study 1 examines the effect of acute stress on cognitive performance in healthy older adults. Study 2 compares the effects of acute stress on physiology, mood and cognition in patients with Parkinson's disease (PD), an age-related neurodegenerative disease characterized by reports of increased stress susceptibility, to that of healthy older adults.

The goal of the first study was to investigate the effect of an online acute psychosocial stressor on working memory and executive function in older adults and to measure sex differences in the effects of acute stress on cognition. The specific objectives were: 1) to determine the effect of acute psychosocial stress, administered in an automated online protocol, on cognitive performance in older adults, specifically in working memory and executive function; and 2) to determine whether the effect of acute stress on cognition in older adults is moderated by sex. To answer these questions, we conducted an online study with older adults who were randomly assigned to either a Stress or Control condition and evaluated the effects of stress on their performance on a spatial working memory task, verbal working memory task and executive function/interference task. To induce psychosocial stress, we created a custom online procedure that adapted elements of standard in-lab stress induction protocols. Our findings showed that the Stress group reported significantly worse mood than the Control group, and that there were generally beneficial effects of stress on cognitive performance that varied by sex.

The goal of the second study was to investigate the effect of acute stress on physiology, mood and cognition in PD patients. The specific objectives were: 1) to determine whether acute laboratory-induced psychosocial stress causes a greater physiological and affective stress response in PD patients relative to healthy older adults; and 2) to determine if acute stress causes cognitive performance impairments in PD patients. To answer these questions, we used the socially evaluated cold-pressor test to induce acute stress and measured stress responses using salivary cortisol, blood pressure and self-reported affect at multiple timepoints. Cognitive performance was

measured before and after the manipulation using a working memory task. We found that healthy older adults and PD patients did not differ in their physiological stress responses but that PD patients showed a blunted affective response to acute stress compared to healthy older adults. We also found that healthy older adults showed a beneficial effect of acute stress on working memory performance, which is consistent with prior research, but PD patients did not show this beneficial effect.

The studies discussed herein explore the nuanced effects of acute stress on healthy older adults and PD patients, shedding light on demographic and clinical factors that could influence stress susceptibility. Our findings also point to stress as a potentially modifiable factor for improvement of cognitive performance in PD patients. Finally, this thesis concludes with a discussion of possible mechanisms for the findings and proposes potential future directions.

Résumé

Le stress aigu est un phénomène omniprésent dans la vie quotidienne, touchant aussi bien les jeunes que les personnes âgées, et il a un impact important sur le bien-être cognitif. Cependant, les recherches sur le stress ont été largement menées auprès de jeunes adultes en bonne santé, et des lacunes importantes subsistent dans notre compréhension de l'impact du stress sur la fonction cognitive des personnes âgées. Cette thèse présente deux études portant sur des populations distinctes: L'étude 1 examine l'effet du stress aigu sur les performances cognitives chez les personnes âgées en bonne santé. L'étude 2 compare les effets du stress aigu sur la physiologie, l'humeur et la cognition chez les patients atteints de la maladie de Parkinson (MP), une maladie neurodégénérative liée à l'âge caractérisée par des rapports faisant état d'une susceptibilité accrue au stress, à ceux des personnes âgées en bonne santé.

L'objectif de la première étude était d'étudier l'effet d'un facteur de stress psychosocial aigu en ligne sur la mémoire de travail et la fonction exécutive chez les personnes âgées et de mesurer les différences entre les sexes dans les effets du stress aigu sur la cognition. Les objectifs spécifiques étaient les suivants: 1) déterminer l'effet du stress psychosocial aigu, administré dans un protocole automatisé en ligne, sur les performances cognitives des personnes âgées, en particulier sur la mémoire de travail et la fonction exécutive; et 2) déterminer si l'effet du stress aigu sur la cognition chez les personnes âgées est modéré selon le sexe. Pour répondre à ces questions, nous avons mené une étude en ligne auprès de personnes âgées assignées au hasard à une condition de stress ou de contrôle et avons évalué les effets du stress sur leurs performances dans le cadre d'une tâche de mémoire de travail spatiale, d'une tâche de mémoire de travail verbale et d'une tâche de fonction exécutive/interférence. Pour induire un stress psychosocial, nous avons créé une procédure en ligne personnalisée qui a adapté des éléments des protocoles standard d'induction du stress en laboratoire. Nos résultats ont montré que le groupe stressé faisait état d'une humeur nettement moins bonne que le groupe témoin et que le stress avait généralement des effets bénéfiques sur les performances cognitives qui variaient selon le sexe.

L'objectif de la deuxième étude était d'étudier l'effet du stress aigu sur la physiologie, l'humeur et la cognition des patients parkinsoniens. Les objectifs spécifiques étaient les suivants: 1) déterminer si le stress psychosocial aigu induit en laboratoire provoque une plus grande réponse au stress

physiologique et affectif chez les patients parkinsoniens par rapport aux personnes âgées en bonne santé; et 2) pour déterminer si le stress aigu provoque des troubles des performances cognitives chez les patients parkinsoniens. Pour répondre à ces questions, nous avons utilisé le test de pression au froid socialement évalué pour induire un stress aigu et mesuré les réponses au stress à l'aide du cortisol salivaire, de la tension artérielle et des effets autodéclarés à plusieurs moments. Les performances cognitives ont été mesurées avant et après la manipulation à l'aide d'une tâche de mémoire de travail. Nous avons constaté que les adultes âgés en bonne santé et les patients parkinsoniens ne différaient pas dans leurs réponses physiologiques au stress, mais que les patients parkinsoniens présentaient une réponse affective atténuée au stress aigu par rapport aux adultes âgés en bonne santé. Nous avons également constaté que les personnes âgées en bonne santé présentaient un effet bénéfique du stress aigu sur les performances de la mémoire de travail, ce qui est cohérent avec des recherches antérieures, mais que les patients atteints de MP n'ont pas montré cet effet bénéfique.

Les études discutées ici explorent les effets nuancés du stress aigu sur les personnes âgées en bonne santé et les patients parkinsoniens, mettant en lumière les facteurs démographiques et cliniques qui pourraient influencer la susceptibilité au stress. Nos résultats indiquent également que le stress est un facteur potentiellement modifiable pour l’amélioration des performances cognitives chez les patients parkinsoniens. Enfin, cette thèse se termine par une discussion des mécanismes possibles pour les résultats et propose des orientations futures potentielles.

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Contribution of Authors

I am the primary author of both manuscripts presented in this thesis (chapters 2 and 3), and in both cases, I share primary authorship with Mario Bogdanov.

In Chapter 2, the study was conceived by my supervisor Madeleine Sharp and by Mario Bogdanov. Léah Suissa-Rocheleau and MB also designed the study and collected the data. I was responsible for data processing, visualization and analysis with input from MB, and wrote the manuscript with input from the other co-authors. In Chapter 3, the study was conceived by MS and MB and designed by myself, MS and MB. I collected the data with the assistance of Lara Ekin Telli and Nasri Balit. I processed, visualized and analyzed the data with input from Mario Bogdanov. I wrote the manuscript with input from the co-authors.

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List of Abbreviations

PD: Parkinson's Disease
HPA: hypothalamic-pituitary-adrenal
SAM: sympathetic-adreno-medullar
PFC: prefrontal cortex
TSST: Trier Social Stress Task
WM: working memory
MDMQ: Multidimensional Mood State Questionnaire
HR: Holmes-Rahe Life Stress Inventory
SD: standard deviation
SNRI: serotonin and norepinephrine reuptake inhibitor
UPDRS: United Parkinson's Disease Rating Scale
OA: older adults
sAA: salivary alpha amylase
MIST: Montreal Imaging Stress Task
ANS: autonomic nervous system
SE-CPT: socially evaluated cold-pressor test
MoCA: Montreal Cognitive Assessment
GDS: geriatric depression scale
PSS: perceived stress scale
RT: response time
delta_GB: change in good-bad score
CAD: Canadian dollar

1 Introduction

Stress is encountered by most people on a daily basis in varying degrees of intensity, impacting their health, mood and cognition. The impact of stress is vastly complex as it interacts with many individual differences such as age and sex and affects healthy and patient populations differently. This thesis encompasses two studies: the first is an online stress induction study which aims to examine the effect of an online acute stressor on healthy middle aged and older adults both affectively and cognitively. The second study is an in-laboratory acute stress induction which aims to examine the effect of acute stress on physiological response, mood and cognition in Parkinson's disease (PD) patients compared to healthy older adults (OAs). Together these studies hope to provide a clearer picture of the effects of acute stress on cognition in OAs and PDs. Investigating the effects of acute stress on physiology and cognition in PD is a completely novel addition to the field since, as far as our knowledge, there have been no studies exploring this in lab conditions.

1.1 The stress cascade

Acute stress is known to cause a cascade of physiological reactions, beginning with the fast-acting sympathetic-adreno-medullar (SAM) system activation, which is followed by the activation of the hypothalamic-pituitary-adrenal (HPA) axis, resulting in a release of several hormones from the adrenal glands, including the stress hormone cortisol (Francis & Meaney, 1999). Cortisol, which crosses the blood-brain barrier, peaks around 25 minutes after stress onset and can have differing effects on a wide range of cognitive processes (Lupien et al., 2005, 2007; Sandi, 2013). The effects of stress on cognition have been extensively researched, especially focusing on certain aspects of cognition such as working memory, attention, and executive function. However, the effect of acute stress on cognition can differ with age and may be moderated by sex.

1.2 The effect of stress on cognitive performance

Acute stress is a daily experience for many people and has documented effects on cognitive processes such as working memory, attention, and executive function (Schwabe et al., 2012; Starcke & Brand, 2012; Wirz et al., 2018), processes that depend on prefrontal cortical regions and networks that are also known to be sensitive to stress (Arnsten, 2009; Bogdanov & Schwabe, 2016; Joëls & Baram, 2009; Liston et al., 2009; Otto et al., 2013; Owen et al., 2005; Sandi, 2013; Schoofs et al., 2008). However, stress effects on cognition are not homogenous across reported studies and

seem to vary between cognitive domains. Even within the same cognitive process, for example working memory, there is evidence of both beneficial effects of stress (van Ast et al., 2016) and detrimental effects of stress (Oei et al., 2006; Schoofs et al., 2008) illustrating the heterogeneity of the current literature. For example, in a study by van Ast and colleagues (2016), participants were acutely stressed using the Trier Social Stress Test (TSST(Kirschbaum et al., 1993)) - a widely used socially evaluative stress induction - and then tested on working memory and showed better performance compared to the control group. On the other hand, a study by Oei and colleagues (2006) investigated the same relationship using the same stress paradigm and found that stress negatively affected working memory performance under high cognitive loads but not under lower cognitive loads. This study also highlights the modulating role of one possible factor, cognitive load, on the effect of stress on cognition by varying the number of stimuli to be held in memory simultaneously. However, the directionality of the effect of cognitive load remains unclear as other studies such as Beste et al (2013) showed that following an acute stress manipulation, the socially evaluated cold pressure task, participants in the stress condition performed better than the controls on a dual-processing, high cognitive load task. Other modulating factors including the type of cognitive process being measured and the magnitude of the cortisol response can non-linearly influence the effect of stress on cognition. While the heterogeneity in the literature may partly be explained by differences in experimental design, recent work has also highlighted the importance of individual characteristics such as intensity of stress, age and sex of the participants for moderating the effects of stress on cognition (Goldfarb et al., 2017; Hidalgo et al., 2019; Schoofs et al., 2013).

1.3 Nonlinear relationship between stress and cognitive performance

Studies suggest that the intensity of stress may influence the effects of stress on cognition in an non-linear manner whereby low to moderate levels of stress have been shown to improve simpler cognitive task performance whereas higher levels of stress detrimentally impact PFC- and hippocampus-dependent cognitive processes (Goldfarb et al., 2017; Kluen, Nixon, et al., 2017; Sandi, 2013; Vogel et al., 2018). These effects resemble the inverted-u shape, first proposed in the form of the Yerkes-Dodson law, which suggests that the ideal performance on more difficult tasks requires optimal levels of stress, and that performance is impaired if stress is above or below this optimal level (Arnsten, 2009; Lupien et al., 2007; Sapolsky, 2015; Yerkes & Dodson, 1908). This

phenomenon can be illustrated clearly by a study in rats' performance on a water spatial memory task. Rats were trained under one of three water temperatures, 16, 19 and 25 degrees Celsius, and they found that the rats at the middle (most comfortable) temperature performing best on the maze with the least number of errors (Salehi et al., 2010). Some studies have suggested that the inverted-u effect of stress on cognition can be attributed to cortisol levels, for example, a study on squirrels experimentally manipulated cortisol levels to be both greater and less than the natural occurring cortisol levels and showed that those deviations had a detrimental effect on learning (Mateo, 2008). Similar cortisol manipulations have been attempted in humans. For instance, in one study, memory recall was tested after an injection of either a placebo or one of varying doses of hydrocortisone (3 mg, 6 mg, 12 mg, 24 mg) and authors found that memory performance was greatest at moderate cortisol levels (Schilling et al., 2013). This inverted u shape was also observed in a different study even when only one dosage of hydrocortisone (25 mg) was administered by splitting participants into high or low cortisol responders depending on measured salivary cortisol after the hydrocortisone (Domes et al., 2005). When a memory test was administered following the oral dosage, the low responders group (participants who showed lesser salivary cortisol increases) showed the best verbal memory recall compared to the high responders and the placebo group, suggesting that there exists an optimal level of stress for memory enhancing effects (Domes et al., 2005). However, it would be naïve to not acknowledge that the existence of this u-shaped curve has been a topic of debate for many years (Mendl, 1999; Muse et al., 2003; Shih & Lin, 2017).

1.4 Stress effects across the lifespan

Traditionally, most stress research has been conducted on younger adults (Hidalgo et al., 2015; Schoofs et al., 2013) although preliminary evidence suggests that the effect of acute stress on cognition is influenced by age. For example, there is evidence that psychosocial stress in older adults is not only less harmful to working memory compared to younger adults (Pulopulos et al., 2015; Schnitzspahn et al., 2022; Wolf et al., 2001) but that it may even be beneficial to memory performance (Hidalgo et al., 2014, 2019). This notion is further supported by a recent meta-analysis investigating the effects of acute stress on cognition in older adults, which found that effects tend to be highly variable, with older adults experiencing positive effects of stress on working memory, negative effects on verbal fluency, negative to null effects on episodic memory and null effects on executive function (Mikneviciute et al., 2022). Some explanations for these

differences could be that different brain regions are required for the same cognitive process in younger compared to older adults (Yaple et al., 2019) or that the difficulty of the task differs with age (Kirchner, 1959). Importantly, these differences are not a result of reduced activation of the HPA axis in older adults as older adults show the same pattern of increased cortisol following acute stress induction as younger adults (Hidalgo et al., 2015). The absence of a detrimental stress effect on working memory was even observed when tested following an oral dose of hydrocortisone in older adults between the ages of 69-82 (Porter et al., 2002), and following an intravenous injection of hydrocortisone in older adults between 51-82 of age (Yehuda et al., 2007). These findings further suggest that age-related differences in cognitive responses to stress are unlikely to be caused by age-related differences in cortisol responses to acute stressors. This literature supports the idea that with increase of age there is a change in the effects of stress on cognition; however, the specific directionality of change on the different cognitive processes remains unclear as studies often point to conflicting results both in older adults (Hidalgo et al., 2014; Luers et al., 2020) and in younger adults (Schoofs et al., 2008; van Ast et al., 2016).

1.5 Sex differences in the effect of stress on cognitive performance

Another important factor influencing the effects of stress on cognition is sex. Studies in young adults have generally found greater physiological stress responses as measured by cortisol in men compared to women, potentially due to differences in the presences of the hormones estrogen and progesterone, which have a mediating effect on stress (Kluen, Agorastos, et al., 2017b, 2017a; Kudielka & Kirschbaum, 2005; Liu et al., 2017). These sex differences are also reflected in cognitive responses to stress. For example, working memory seems to be more susceptible to stress in young men than in young women, though the direction of this difference is variable across studies (Schoofs et al., 2013; Zandara et al., 2016). In the 2013 study by Schoofs and colleagues, after exposure of 59 young adults (mean age = 23) to the Trier Social Stress Task, there was no difference in physiological stress response as measured by salivary cortisol however stress enhanced working memory performance in men but impaired it in women. In contrast, the study by Zandara and colleagues (2016), also using the TSST on young adults, showed that while men had significantly greater cortisol levels, the women rather than the men showed WM improvement following stress. Progesterone and estrogen, which are found in higher concentrations in younger women, often blunt the stress response both in terms of physiological changes and effects of stress

on cognition, as was observed in elderly women using hormone replacement therapy (Herrera et al., 2017; Kudielka et al., 1999; Lindheim et al., 1992). In a 2017 study, 42 post-menopausal women were brought in for two counterbalanced stress and control sessions with working memory testing after the manipulation. Half of the participants had been using estradiol therapy for a median of 4.7 years before the study while the other half received a placebo treatment at the time of the study. Stress was induced using the cold pressor task and the results showed that the women in the estradiol therapy group showed a blunted cortisol response to stress and less negative effects on working memory compared to the placebo group (Herrera et al., 2017). Overall, the literature supports the presence of sex differences in acute stress responses which have mainly been attributed to female reproductive hormones, which also fluctuate across the lifespan.

The influence of sex on the physiological and cognitive effects of stress in older adults is much less understood and is complicated by known sex differences in age-associated cognitive decline (Gur & Gur, 2002; Hidalgo et al., 2015, 2019). Upon comparing the stress responses of older men and women, it was found that men exhibit a greater increase in cortisol levels compared to women (Hidalgo et al., 2015; Kudielka & Kirschbaum, 2005) and greater age-associated cognitive decline (Gur & Gur, 2002) although women showed a greater effect of aging on their cortisol levels (Otte et al., 2005). This change in stress response in women with age can be observed in greater heart rate and blood pressure changes in response to stress and is likely due to the decrease in estrogen and progesterone levels during menopause (Saab et al., 1989). Finally, a few recent studies have started to explore the interaction of sex, cortisol and working memory performance in older adults, and have suggested that following psychosocial stress, women show a dose dependent positive relationship between cortisol levels and working memory performance (Luers et al., 2020; Pulopulos et al., 2015) while men show a negative relationship (Luers et al., 2020).

1.6 Online stress research

While these initial reports exemplify the need to investigate the impact of factors such as age and sex on the effects of stress on cognition, the generalizability of their findings has been limited because of relatively small (many less than 30 participants) and selective samples, with many studies often choosing only male participants to avoid menstrual cycle effects. Recently, with the increased accessibility of technology to both researchers and the general population, there has been

growing interest in turning to online data collection to overcome these shortcomings of in-person experiments. However, given that a key element of many established stress-induction paradigms involves a social interaction, developing online adaptations of these procedures has been challenging. Two recent studies induced acute psychosocial stress using an online adaptation of the TSST through online video conferencing. These studies included physiological and subjective measures of stress in the form of self-measured heart rate, one through a wearable ECG device and the other using a phone application, and self-reported mood. Both studies found a significant increase in heart rate variability and subjective stress ratings for the stress groups (Eagle et al., 2021; Harvie et al., 2021). Although these are successful online adaptations of stress induction techniques, both studies still required at least one experimenter to be present online during the time of the experiment (via live video call), which may limit the potential of the procedure to efficiently achieve large sample sizes. In contrast, another study successfully induced self-reported stress online using the Montreal Imaging Stress Task (MIST) where participants would answer general knowledge and math questions either under time pressure and while receiving negative feedback (Stress condition) or with no time pressure nor feedback (Control condition). Unlike the previous two studies, this methodology did not require the presence of an experimenter online (Almazrouei et al., 2022), taking advantage of the benefits provided by remote online testing. While the sample size was larger than in traditional experiments (n = 118) the average sample age was quite young (mean age = 33) and therefore this study could not explore the mediating effects of age on the relationship between stress and cognition. There has not been an online acute stress induction study in older adults, which presents a separate set of challenges since it is possible that older adults might have somewhat lower computer literacy and that merely participating in an online study could lead to stress, thus potentially reducing observable stress effects. However, given the potentially diverging effects of stress in older adults, including this population in large-sample online studies may help to generate valuable insights into how stress specifically affects cognition and behavior with age.

1.7 Parkinson's disease, stress and cognition

A better understanding of the effects of aging on the cognitive effects of stress also has important implications for better understanding the effects of stress in age-related neurodegenerative disorders like Parkinson's disease. Parkinson's disease, which is a disease characterized by a wide

range of motor, cognitive and mood symptoms, is interestingly also generally thought to be associated with an enhanced sensitivity to stress. However, as of yet, no study has formally investigated the extent to which this is true.

Anecdotally PD patients report high levels of stress, and interestingly, have been noted by neurologists to be very sensitive to stress, suggesting an increased susceptibility to stressors. A recent study of 5000 PD patients reported significantly greater subjective stress reports compared to healthy controls (van der Heide, Speckens, et al., 2021). Furthermore, PD patients have exhibited high susceptibility to stress with studies showing that worsening of motor symptoms such as tremor or gait difficulty can be reliably triggered by stress (Dirkx et al., 2020; van der Heide, Speckens, et al., 2021). Similarly, since stress causes a worsening of motor symptoms, it is probable that it would have a similar effect on cognitive symptoms. However, no studies have systematically measured, under controlled conditions, the physiological effects of acute stress in Parkinson's patients. Therefore, it remains unknown whether the increased motor symptoms induced by stress are merely a function of the motor deficit, or if they indicate that the physiological stress response in PD patients is exaggerated. A 2019 systematic review found that out of 14 studies measuring cortisol, half of them showed that PD patients had elevated cortisol levels which were associated with worsened motor symptoms and affective symptoms however the relationship of cortisol and cognition in PD remains unclear (Soares et al., 2019). Understanding the impacts of stress in PD is especially important given that many of the mood and cognitive symptoms of PD are also those that are influenced by stress.

In addition to the well-studied motor symptoms of Parkinson's disease (PD), cognitive symptoms and specifically cognitive decline play a large role in the dysfunctional nature of the disease. A longitudinal study showed that approximately fifty percent of patients had developed mild cognitive impairment after six years (Pigott et al., 2015). Parkinson's disease (PD) patients show deficits across multiple types of cognitive functioning, including executive functioning, visuospatial functioning and memory (Dubois & Pillon, 1996; Marinus et al., 2003; Poletti et al., 2012). In addition to deficits in working memory, studies show that PD patients also show a blunted reward sensitivity as well as a slower ability to learn through reward learning (Dubois & Pillon, 1996; Timmer et al., 2017). This change in reward sensitivity can be further impacted by

affective disorders such as depression with are also very prevalent in PD (Poletti et al., 2012). In a study by Timmer and colleagues examining PD patients with and without depression history, patients with a history of depression exhibited worse reward vs punishment learning and showed reduced activity in the putamen, a region involved in reward learning (Timmer et al., 2017). Executive functioning also seems to be impaired whereby PD patients underperformed on the Stroop task both in terms of cognitive inability to inhibit as well as in terms of motor responses (Hsieh et al., 2008; Pirogovsky-Turk et al., 2017). A 2017 longitudinal study followed 68 PD patients and 30 healthy older adults over a two year period assessing various different cognitive processes and found that PD patients showed significant decline in learning and executive control as calculated by a difference from baseline score (Pirogovsky-Turk et al., 2017).

1.8 Rationale and objectives

Acute stress is a ubiquitous feature of everyday life, affecting young and old alike, and it has an important impact on cognitive well-being. However, stress research has largely been conducted in healthy, young adults, and important gaps remain in our understanding of the impact of stress on cognitive function of older adults. This thesis encompasses two studies which, together hope to provide a clearer picture of the heterogeneous effects of acute stress on cognition in OAs and PDs which could potentially unveil the need for tailored approaches to understanding and managing stress-related issues, especially in neurodegenerative diseases like PD.

In Chapter 2 we investigated the effect of an online acute psychosocial stressor on working memory and executive function in older adults and measured sex differences in the susceptibility to stress. The specific objectives were the following:

1. To determine the effect of acute psychosocial stress, administered in an automated online protocol, on cognitive performance in older adults, specifically in working memory and executive function.
2. To determine if the effect of acute stress on cognition in older adults moderated by sex.

In Chapter 3 we investigated the effect of acute stress on physiology, mood and cognition in PD patients. The specific objectives were the following:

1. To determine whether acute laboratory-induced psychosocial stress causes a greater physiological and affective stress response in PD patients relative to healthy older adults.
2. To determine if acute stress causes cognitive performance impairments in PD patients.

2 Online acute stress induction in middle and older-aged adults shows beneficial effects on cognition that vary by sex

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Key words: acute stress, executive function, aging, cognition, online

2.1 Abstract

Acute stress is a ubiquitous feature of everyday life, affecting young and old alike. Though it is generally thought to exert detrimental effects on executive functions, the effects of acute stress on cognitive processing have largely been studied in younger, college-aged populations. In this study we tested the effects of acute stress on working memory and executive control in a large sample of male and female middle and older-aged participants using a fully remote online stress paradigm. Participants (n=132, age: 43-74) were randomly assigned to either a Control or Stress condition, which consisted of a challenging arithmetic task with false normative feedback and distressing videos. All participants rated their affective state and perceived stress levels throughout the experiment. To evaluate the effects of stress on cognitive performance, participants completed a spatial working memory task (Corsi block tapping) before and after the manipulation as well as a verbal working memory task (n-back) and executive control task (Stroop color-word interference) after the manipulation. As expected, the Stress group reported significantly worse mood than the control group, indicating the effectiveness of our online protocol, and we found a generally beneficial effect of stress on cognitive performance, though, notably, stress-induced benefits varied by sex in a task-dependent manner. Our results suggest that in middle and older aged adults acute stress is generally associated with improvements rather than impairments in executive function, which may reflect the ability to recruit additional resources for cognitive processing in a way that is sex dependent.

2.2 Introduction

Running late for work, studying for an important exam, or waiting for the results of a medical check-up – these are examples of common daily life situations that may elicit the experience of acute stress. When faced with a potential stressor, our body responds with a complex, time-dependent neuroendocrine reaction that results in a quick and relatively short-lived secretion of monoamines (e.g., noradrenaline and dopamine) through the autonomic nervous system (ANS) and a slower, more gradual secretion of glucocorticoids (i.e., cortisol in humans) through the hypothalamic-pituitary-adrenal (HPA) axis, which affect neural processing across multiple brain networks and, in turn, a wide range of cognitive processes and behaviors (Francis & Meaney, 1999). For example, while acute stress is thought to increase attention to and encoding of stress-relevant stimuli in the environment, acute stress has also been shown to impair cognitive effort and core executive functions, such as working memory, response inhibition, and set-shifting (Arnsten, 2009; Bogdanov et al., 2021; Joëls & Baram, 2009; Lupien et al., 2007; Qin et al., 2009; Sandi, 2013; Schoofs et al., 2009). This is consistent with the idea that stress leads to an overall shift away from top-down regulated, goal-directed processing toward less resource intense, and more habitual forms of behavioral control (Braun & Hauber, 2013; Goldfarb et al., 2017; Otto et al., 2013; Plessow et al., 2012; Schwabe & Wolf, 2010, 2011; Wirz et al., 2018).

However, much of this prior work focuses on investigating stress effects in mostly young, healthy, and well-educated groups using in-laboratory experiments that can create barriers to accessibility and limit the potential sample size. As such, findings from these studies may have limited generalizability for the broader population. For example, preliminary evidence suggests that the impact of acute stress on cognition may be different in older compared to younger adults. More specifically, some findings suggest that middle aged and older adults are less impaired by, and may even benefit from acute stress in the domains of working memory (Pulopulos et al., 2015; Schnitzspahn et al., 2022; Wolf et al., 2001) and declarative memory (Almela, Hidalgo, Villada, Espín, et al., 2011; Hidalgo et al., 2014, 2019). Importantly, these different stress effects on cognition are unlikely to result from a dampened activation of the HPA axis in older adults as they show the same pattern of increased cortisol following acute stress induction as younger adults (Hidalgo et al., 2015; Seeman et al., 2001). More broadly however, the effect of stress in middle-

aged and older adults is not entirely clear, as demonstrated in a recent meta-analysis that showed that reported stress effects on cognition in older adults are highly variable and often in opposing directions across studies, possibly due, in part, to relatively small samples and an inability to examine factors, such as sex, that might modulate the effects of stress on cognition (Almela, Hidalgo, Villada, Espín, et al., 2011; Kudielka & Kirschbaum, 2005; Mikneviciute et al., 2022). It thus remains important to further characterize how stress affects older adults, especially given the role of acute stress in the etiology and exacerbation of common psychiatric disorders such as depression and anxiety, which are common throughout the life span (Bibbey et al., 2013; Grynderup et al., 2013; Puig-Perez et al., 2016; Young et al., 2000).

To increase sample sizes and to more easily reach older and more diverse populations, researchers have started to collect data in online experiments (Almazrouei et al., 2022; Eagle et al., 2021; Norden et al., 2022). However, investigations of acute stress have been much less widely conducted online because acute stress manipulations typically include a psychosocial stress (e.g., performance of an oral presentation) and/or a physical stress (e.g., immersing hand in cold water), both of which usually necessitate the physical presence of experimenters. Interestingly, some recent studies suggest that the online induction of acute psychosocial stress is feasible, and reliably causes an increase in self-reported stress and an increase in physiological markers including heart rate, cortisol and alpha amylase. Several of these studies have used an adaptation of the Trier Social Stress Test (TSST; Kirschbaum et al., 1993) and have therefore relied on video conferencing for the oral presentation element of the manipulation, thereby significantly limiting potential scalability (Eagle et al., 2021; Gunnar et al., 2021; Harvie et al., 2021; Meier et al., 2022). In contrast to the online studies that require researcher presence via video conferencing, a few recent studies have moved towards stress manipulations that completely eliminate the need for a interaction with a researcher and have showed successful remote stress induction in younger adults based on self-report measures (Almazrouei et al., 2022; Norden et al., 2022). Whether a fully remote online stress manipulation can successfully be used in older adults to induce stress remains unknown.

Here, we aimed to assess the effects of an online and unsupervised acute psychosocial stress manipulation on self-reported mood, self-reported stress and cognitive performance in middle-

aged and older adults. The psychosocial stress manipulation combined an online adaptation of the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) and unpleasant videos. Self-reported mood, stress and cognitive performance were recorded before and after the stress and control manipulations. For cognitive evaluations, we focused on working memory and executive function because prior literature points to the fact that these domains are particularly sensitive to stress (Mikneviciute et al., 2022). We hypothesized that the online acute stress manipulation would result in worse mood and increased self-reported stress, and more importantly, that this stress induction would impact cognitive performance. Finally, because prior work in both young and older adults has shown sex differences in both the physiological (Hidalgo et al., 2015; Kudielka & Kirschbaum, 2005; Luers et al., 2020) and cognitive (Kluen, Agorastos, et al., 2017b, 2017a; Pulopulos et al., 2015; Schoofs et al., 2013; Zandara et al., 2016) responses to stress, we stratified our analyses by sex.

2.3 Methods

Participants: We recruited a sample of 275 adults between the ages of 43-75 via Prolific (www.prolific.co). Individuals who were not fluent in English, who had chronic health conditions, current active psychiatric disorders and neurological disorders were ineligible to participate. We planned this sample anticipating significant data exclusions given the online nature of the study. 139 participants were excluded for incomplete data and one additional participant was excluded for falling outside of the age range. Further exclusions were made on a task-by-task basis as described below. Participants were randomly assigned to either the Stress or the Control condition and the final sample consisted of 132 participants: 63 assigned to the Control condition (mean age: 51.4, 51% male) and 69 assigned to the Stress condition (mean age: 52.3, 39% male), allowing us to detect a between group difference with an effect size of at least 0.6 with 90% power (Faul et al., 2007). All participants provided informed consent at the start of the experiment and received a compensation of 9.5 CAD/hour in accordance with the recommended pay scale on Prolific at the time of testing. Importantly, participants were unaware that the study was specifically about stress as the consenting procedure merely indicated that this was a study about emotions. All participants were debriefed at the end about the true nature of the study. All procedures were approved by the McGill University Health Centre Research Ethics Board.

Table 2-1: Participant characteristics

	Stress **(n = 69)**	Control **(n = 63)**	p-value
Age	52.3 (6.45, 43-68)	51.4 (5.53, 45-74)	0.36
Sex (#males/ females)	26/43	32/31	0.13
Education (years)	15.7 (2.91, 11-23)	16.1 (2.58, 11-24)	0.35
Geriatric Depression Scale	3.4 (4.19, 0-15)	2.6 (2.88, 0-14)	0.24
Perceived Stress Scale	12.3 (6.89, 0-30)	14.2 (6.41, 1-35)	0.10
Holmes-Rahe Life Stress Inventory	131.8 (129.9, 0-712)	142.0 (142.3, 0-805)	0.67

Values represent mean (SD, range).

Manipulation

Stress condition: The stress manipulation was a combination of an adaptation of the MIST followed by five unpleasant videos. The first part of the acute stress manipulation was an online adaptation of the Montreal Imaging Stress Task (MIST; Almazrouei et al., 2022; Dedovic et al., 2005) and consisted of difficult math problems under time pressure with false normative feedback to induce evaluative stress (**Figure 1**). Participants were provided the following false information at the time of starting the task and which was also meant to induce stress: "over 90% of people who have done this math game are able to finish on time", that they "should be able to do so as well!" and that they "must achieve a minimum of 85% accuracy to be included in the study". Participants completed four two-minute blocks of math problems (additions, subtractions, multiplications and divisions) with a varying time allocation of 6-15 seconds to solve the problems. A time countdown was presented on-screen to enhance the time pressure. This timer updated to ensure participants were given less time than they required by checking the accuracy of the two most recent trials. If both trials were correct, the time limit was reduced by 90%. If only one of the two trials were correct, the time limit remained the same. If neither trial was correct, the time limit was increased by 5%. Answers to all math problems were numbers between 0 and 9 so that responses had to be provided by clicking the correct number on the on-screen number wheel, which

involved additional effort and time elements because participants had to sequentially click each digit up until the correct one. A 3 second, unpleasant screeching sound was also played during the majority of trials at randomly selected points. The likelihood of the sound playing was 67% for trials of 6 second length, 60% for 7 second trials and 64% for trials longer than 7 seconds. Feedback falsely indicating that they were underperforming compared to other participants was shown after every trial. The second part of the stress manipulation consisted of viewing five short unpleasant videos (approximately 1 minute each) selected from publicly available news clips depicting high stress situations (footage of severe airplane turbulence, jail violence, hidden camera footage of babysitter screaming at child, extreme roof jumping, train chase in a tunnel).

Control condition: The overall structure and duration of the control manipulation was identical to that of the stress manipulation. However, math problems were easier (one rather than two arithmetic operations, on smaller numbers), without the added time pressure, without false normative feedback and without the unpleasant sounds. The five 1-minute videos depicted neutral footage (earth space, snail moving, butterfly with calming music, turtles swimming, close up of animals).

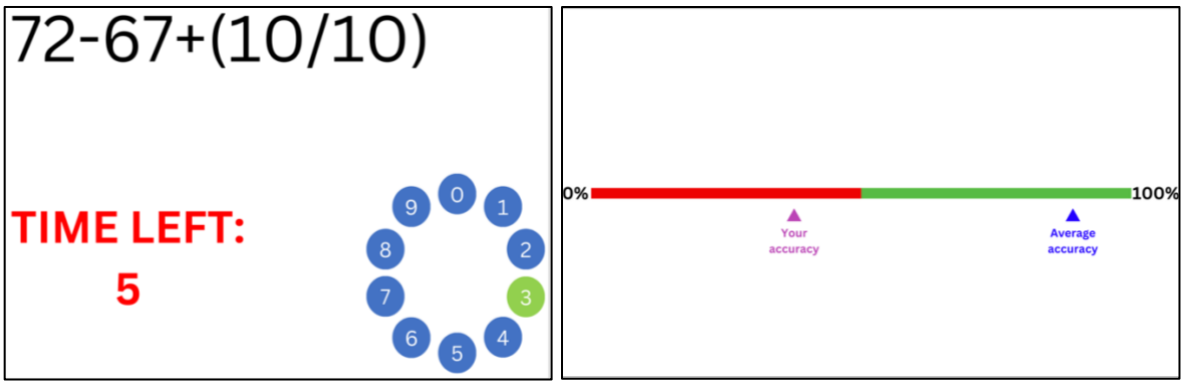

Figure 2-1. Stress condition math task. The stress condition math task was adapted from the Montreal Imaging Stress Task (MIST,(Dedovic et al., 2005)). Participants were shown a math problem consisting of two arithmetic operations. Participants provided the solution to the math problem by selecting the number corresponding to the solution on the rotary dial and, to do so, had to use the forward arrow key to advance digit-by-digit around the wheel. An on-screen timer counted down the seconds left. A feedback screen provided false feedback about the participant's performance relative to average performance on the task, and always depicted the participant as performing worse than the average.

Mood measures pre- and post-manipulation

Mood ratings were recorded before the manipulation, immediately after, and at the end of the study using a shortened English version of the Multidimensional Mood State Questionnaire (Eid et al., 1994; Steyer et al., 1997). This version included the eight questions from the calm-nervous subscale and eight questions from the good-bad subscale, which have previously been shown to be sensitive to acute stress manipulations (Bogdanov & Schwabe, 2016; Cahlíková & Cingl, 2017; Het & Wolf, 2007). Immediately following the manipulation, participants were also asked three questions regarding how stressed, calm and pleased they felt with respect to the stress or control manipulations they had just experienced. Unlike the MDMQ, these questions were only asked after the manipulation so as to not unveil the purpose of the study. All responses were recorded on a sliding scale and numerically coded from 0 to 100.

Cognitive tasks

Working memory: The Corsi block tapping task and the two-back task were administered as measures of spatial and verbal working memory, respectively, as performance on these tasks has previously been shown to be sensitive to acute stress (Bogdanov & Schwabe, 2016; Geißler et al., 2023). In the Corsi block tapping task (Corsi, 1972), administered before and after the manipulation, a series of squares are presented at various locations on screen and sequentially flash red in a random order. Participants are asked to click on the squares in the order that they flashed. Seven levels of difficulty are assessed starting at three squares, and up to nine squares, with two trials per level. To move on to the next level, the participant must get at least one of the two trials correct. The task ends if both trials of a level are answered incorrectly. To reduce practice effects, different location sequences were used at each timepoint. The outcome measure of the corsi block tapping task is weighted accuracy which is computed as seen in equation 1 where the total number of correct responses is added, each of which is weighted at 50 points, then multiplied by the highest correct level reached (ie the level where at least one of the two trials was correct) divided by the total number of possible levels (14) each weighted at 50 points. The weighted accuracy score was computed in order to account for both number of correct trials as well as the maximum level (i.e. span) reached. Exclusions were established based on clearly observed technical errors: if a participant had 0 correct answers in either timepoint, both of the timepoints of that participant were excluded. This led to the exclusion of 6 participants (4 from control group, 2 from stress group).

Data were lost for an additional 38 participants. The final sample for the Corsi analyses was 42 in the control group and 46 in stress group.

$$Acc_{weighted} = \frac{\Sigma correct\ responses \times 50 \times level_{highest\ correct}}{700} \qquad (1)$$

Equation 2-1: Weighted accuracy calculation for corsi block tapping task. This formula calculates an accuracy score for corsi that incorporates both the number of correct trials and the level reached to create a more holistic measure of success on the task.

The two-back task (Conway et al., 2005; Kane & Engle, 2002) was administered only after the manipulation and consisted of a series of 70 letters flashing on screen one at a time. The participant was required to indicate whether the letter currently on screen was the same (21 target trials) or different (49 non-target trials) from the letter that appeared two trials ago. Maximum response time was 2000 ms. 127 entries were received (63 control, 64 stress) but one participant was excluded due to >50% of trials being unanswered. Trial level exclusions were made whereby a trial was excluded if the response time for that trial was 2.5 standard deviations above or below the participant's average response time. Subject level exclusions consisted of excluding participants with a target accuracy below 30% (excluded 2 from control, 1 from stress) and excluding participants who had both a target accuracy and non-target accuracy score below 50% (excluded 1 from control, 2 from stress). Overall, 7 participant exclusions were made, leaving the final sample for the two-back analyses as 60 in the control group and 60 in stress group.

Executive control: The color-word Stroop task was administered only after the manipulation (Stroop, 1935). The task consisted of a series of color words ('red', 'blue', 'green') that were presented on screen either in the same font color as the word (congruent trials, 90/120 trials) or in a different color (incongruent trials, 30/120). The participant was required to indicate the color of the font using one of three keyboard keys. Maximum response time was 2000 ms. 127 entries were received (63 control, 64 stress). Any timed-out trials were removed and trial level exclusions were made whereby a trial was excluded if the response time for that trial was 2.5 standard deviations above or below the participant's average response time. Subject level exclusions consisted of excluding participants with an incongruent accuracy below two standard deviations from the sample's mean incongruent accuracy (excluded for incongruent acc < 51%). Overall, 6 participant

exclusions were made (4 control, 2 stress), leaving the final sample for the Stroop analyses as 59 in the control group and 62 in stress group.

Procedure: The procedure is described in Figure 2. Participants completed a demographics questionnaire followed by a sound check, which consisted of 5 multiple choice questions presented after a sound was played, to ensure their speakers were functioning. Baseline mood (MDMQ) and working memory (Corsi block tapping) were tested following which, depending on random group assignment, either the stress or control manipulations were administered, as described above. Immediately after the manipulation, mood and stress were tested. To ensure that post-manipulation cognitive testing was conducted only after the hypothesized increase in cortisol had occurred, i.e. after about 10-20 minutes (Kudielka et al., 2004), a timer kept track of time since the end of the manipulation. If 10 minutes had not passed, a series of easy filler tasks (drag and drop puzzle, an English proficiency test and the muller lyre illusion) were administered as needed to complete the 10-minute window. Performance on these tasks was not used in analyses. After this 10-minute window, participants completed the cognitive tasks in the following fixed order: the second instance of the Corsi task, the two-back task and the Stroop task. Following this, participants filled out the third instance of the MDMQ. Finally, participants also completed questionnaires assessing depression (Geriatric Depression Scale, GDS; Montorio & Izal, 1996), perceived stress in last month (Perceived Stress Scale, PSS; Lee, 2012) and lifetime stress (Holmes-Rahe Stress inventory; Noone, 2017) before receiving a full debrief of the purpose of the study.

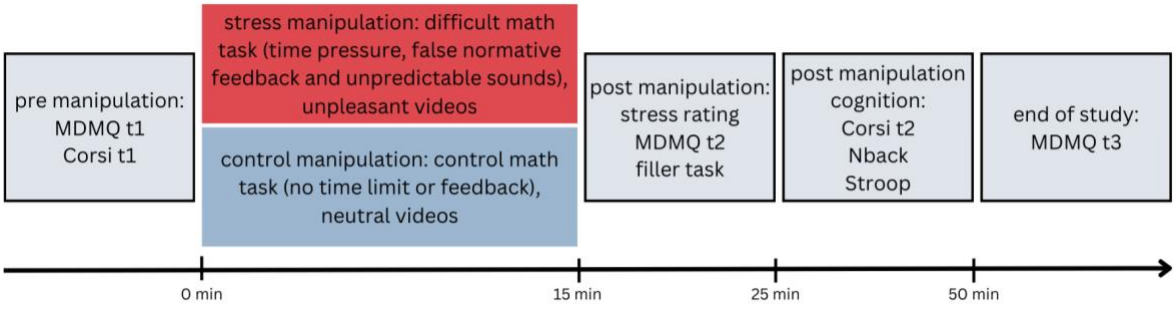

Figure 2-2. Schematic of the experimental procedures and timeline. Participants were randomly assigned to either the stress or control condition.

Data Analysis

Subjective stress scores from the post manipulation question and self-reported mood from the MDMQ were analyzed using a linear regression with group (control vs. stress) and sex (male vs. female) as predictors, including their interaction. Group differences in the change in self-reported mood (MDMQ scores timepoint 2 - timepoint 1) were analyzed with a two-way mixed-model ANOVA with group, timepoint (within-subject factor), and their interaction. Group differences in Corsi span task performance (subject-level computed weighted accuracy) were analyzed using a three-way ANOVA with group, timepoint (within-subject factor) and sex in addition to their interactions. For ANOVAs, we report Greenhouse-Geisser corrected F-values if sphericity is violated. Significant interaction terms are followed up by appropriate post-hoc comparisons. Analyses of nback and Stroop performance were conducted on trial-level data and employed mixed effects models. Group differences for performance on the nback (trial-level accuracy) and Stroop (log transformed correct response times) were analyzed using logistic and linear mixed effects models respectively with group (control/stress, coded as -1/1), sex (male/female, coded as -1/1) and trial type (non-target/target for n-back and incongruent/congruent for Stroop) as well as all their interactions as fixed effects. Mixed models also included random intercepts for subject and trial-level predictors that varied within subject as random slopes. All analyses were performed in R (version 4.1.2) using R Studio (2021.09.1+372) with the built-in t-test and ANOVA functions, the lme4 (1.1-30) package and some repeated measures ANOVAs used the rstatix (0.7.2) package.

2.4 Results

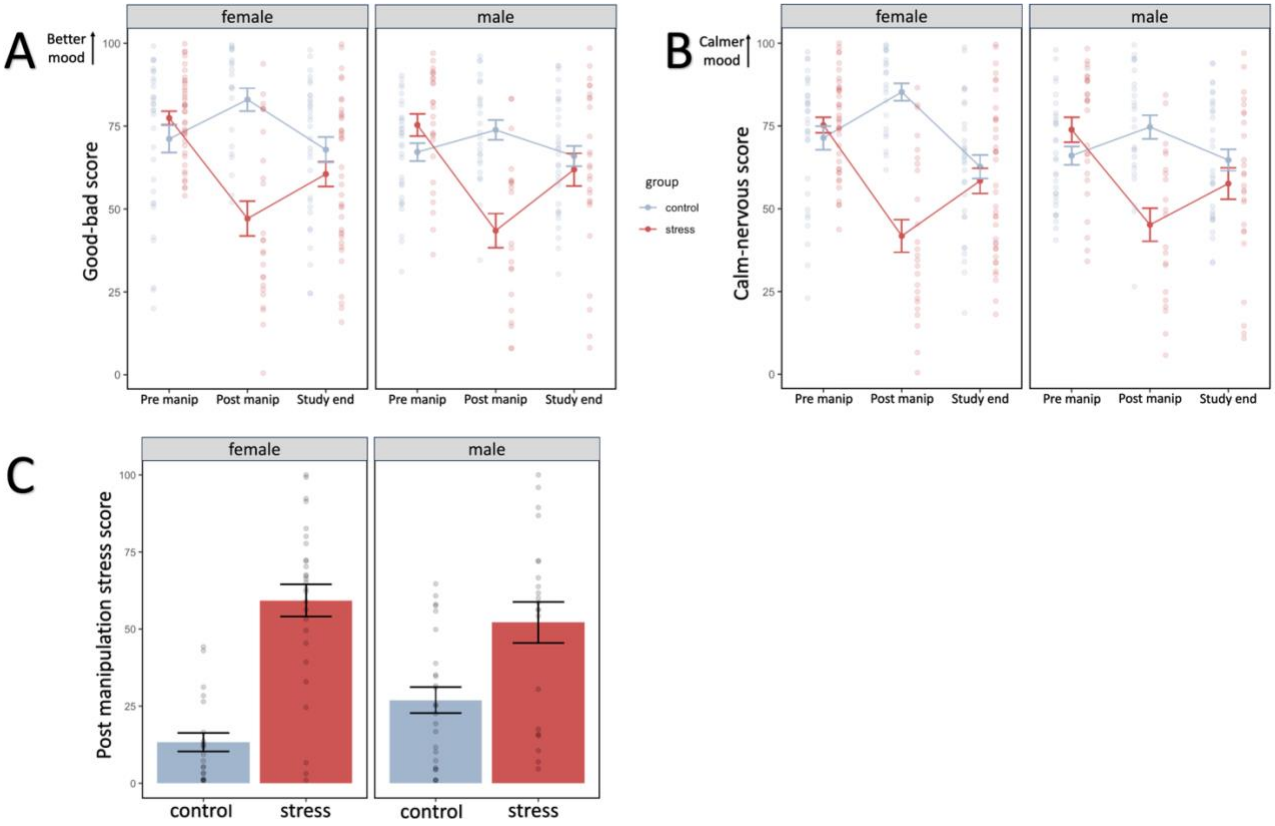

Figure 2-3. The effect of stress on self-reported mood. A) Scores on the Good-Bad subscale of the MDMQ, where a higher score represents better mood, and which were collected before the manipulation, immediately after and at the end of the study. Females and males are shown separately. B) Scores on the Calm-Nervous subscale of the MDMQ, which were collected at the same timepoints, shown separately for females and males. On both scales, we found a significant group*timepoint effect (ps <.001) with mood being worse after the stress manipulation compared to the control group (ps<.001). C) Score on the single question that asked "How stressed do you feel right now", which was presented immediately after the manipulation, split by sex. The stress group reported significantly greater levels of stress than the control group (p<.001), and this effect was more enhanced in female than male participants (p=0.04). MDMQ = multidimensional mood questionnaire Error bars represent standard error of the mean.

<u>Effect of online acute stress on self-reported mood</u>

We first sought to determine if the online stress manipulation caused a worsening of mood and if the effect differed between sexes. Since the MDMQ was collected at three timepoints (before, immediately after the manipulation and at the end of the study), we used a three-way ANOVA (group*timepoint*sex), and found a significant main effect of group ($F_{group}(2,336)=13.6$, $p<.001$), a significant main effect of timepoint ($F_{group*time}(2,336)=10.6$, $p<.001$) and a group*timepoint interaction effect on the Good-Bad subscale ($F(2,336)=27.4$, $p<.001$; **Figure 2-3A**). These effects

were also replicated on the Calm-Nervous subscale ($F_{timepoint}(2,336)=12.2$, $p<.001$; $F_{group}(2,336)=19.4$, $p<.001$; $F_{group*time}(2,336)=31.8$, $p<.001$; **Figure 2-3B**). There was no main effect of sex, nor any interactions with sex. Post-hoc t-tests showed that, on both subscales, mood was worse in the stress group than the control group when measured immediately after the manipulation ($t_{good-bad}=-7.49$, $p<.001$, $t_{calm-nervous}=-8.56$, $p<.001$), and that mood in the stress group was significantly worse at timepoint 2 than timepoint 1 ($t_{good-bad}=7.64$, $p<.001$, $t_{calm-nervous}=7.80$, $p<.001$). Finally, we compared the change in mood (timepoint 2 – timepoint 1) between groups on each subscale and found a significantly greater worsening of mood in the stress group compared to the control group on both subscales ($t_{good-bad}=-10.4$, $p<.001$, $t_{calm-nervous}=-11.1$, $p<.001$). Immediately after the manipulation, participants also answered a single question asking them "How stressed do you feel right now?", which was included only at this timepoint so as to not reveal the purpose of the procedure to them. We ran a linear regression on stress scores and found a significant main effect of group ($\beta=17.8$, $p<.001$) and significant group*sex interaction effect ($\beta=5.2$, $p=.04$) on stress score indicating higher stress in the stress group compared to the control group, and an enhancement of this difference in female compared to male participants (**Figure 2-3C**).

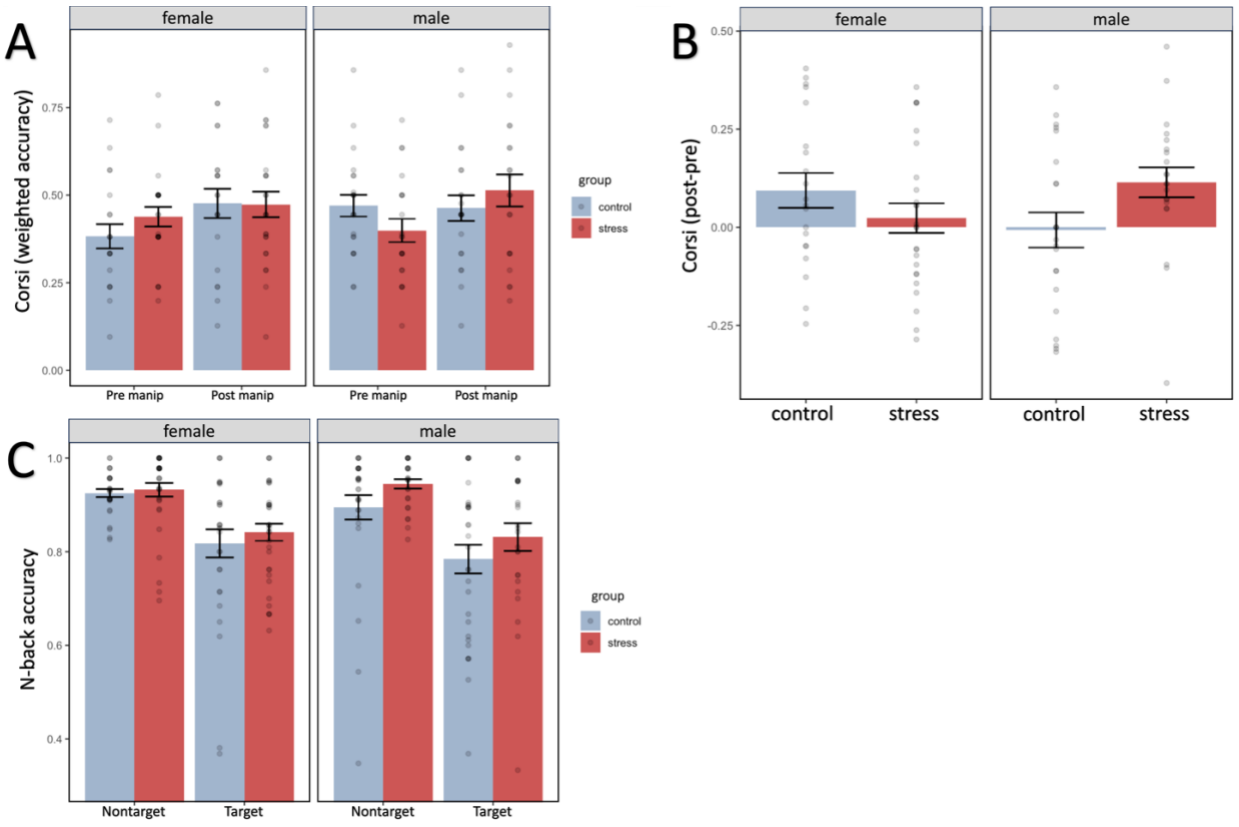

Figure 2-4. Effects of acute stress on working memory performance. A) Corsi performance indicated by weighted accuracy scores split by timepoint, sex and group. B) Corsi change in performance scores (post-pre) indicated by weighted accuracy scores split by sex and group. C) Two-back accuracy scores split by sex, group and trial type. Error bars represent standard error of the mean.

2.4.1 Effect of online acute stress on working memory

To assess the effect of acute stress on spatial working memory, which was measured before and after the manipulation, we conducted a three-way ANOVA (timepoint*group*sex) on the weighted accuracy scores of the Corsi block tapping task. There was no main effect of group ($F_{group}(1,83)=0.073$, $p=0.79$), nor a timepoint*group interaction ($F_{time*group}(1,83)=0.58$, $p=0.45$), but there was a timepoint*group*sex interaction ($F_{time*group*sex}(1,83)=4.76$, $p=0.032$) (**Figure 2-4A**). Visually we saw that male participants in the control session showed slight nonsignificant worsening in performance but under stress showed significant improvement ($t_{stress-male}=-2.98$, $p=0.007$). Female participants showed a slight, non-significantly different improvement in the stress group and a slight significantly different improvement in the control group ($t_{control-female}=-2.12$, $p=0.047$). A two-way ANOVA (group*sex) was conducted as a post-hoc on the change in weighted accuracy scores (post minus pre-manipulation) where a significant group*sex interaction

was observed ($F_{group*sex}(1,84)=5.4$, $p=0.023$) indicating that male participants showed a greater Corsi performance improvement than female participants after the stress manipulation compared to the control manipulation (**Figure 2-4B**). As a follow up, we ran t-tests between the stress and control groups for each of the sexes separately and found that, in men, performance improved significantly more after stress than after the control manipulation ($t=-2.06$, $p=0.046$). In female participants, though the change in performance did not significantly differ between the stress and control groups ($t=1.21$, $p=0.23$), numerically, the pattern was opposite to that of the men. See **Supplementary Table 4** for summary of ANOVAs and t-test outputs. Overall, these results indicate that acute stress effects on spatial working memory performance were sex-dependent: acute stress caused an improvement in performance in male but not in female participants.

Verbal working memory was measured only once, after the manipulation using the two-back task. We ran a mixed effects logistic regression on trial-level accuracy and included group, sex and trial type (target and non-target) as effect-coded predictors. In addition to the expected main effect of trial type ($\beta_{Target}=-0.59$, $p<.001$), we found a significant main effect of group ($\beta_{group}=0.17$, $p=0.04$) such that across target and non-target trials, participants in the stress group performed better than participants in the control group (**Figure 2-4C**). There was no significant main effect of sex, nor a significant sex*group interaction. Regression coefficients are presented in **Supplementary Table 5**. Considering data from both working memory tasks, our results suggest a beneficial effect of stress on working memory performance that may be more pronounced in men.

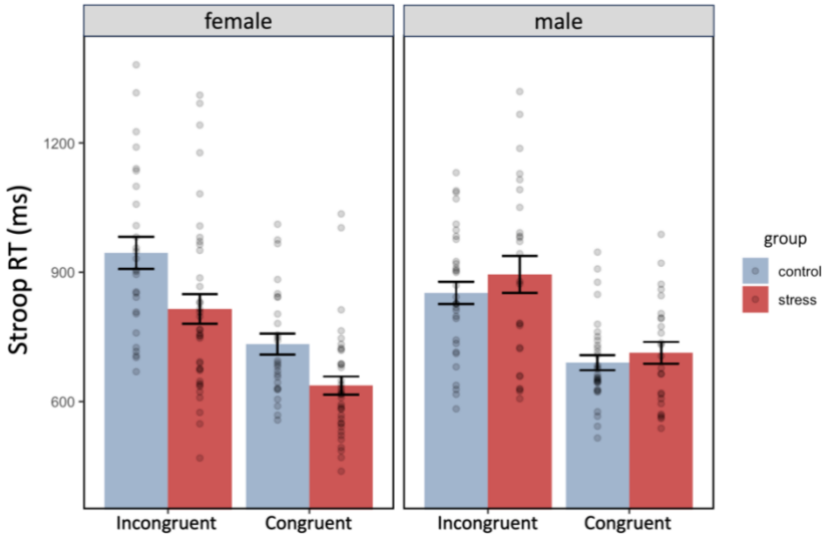

Figure 2-5. Effects of acute stress on Stroop task performance. Stroop task response time split by sex, group and trial type. Error bars represent standard error of the mean.

2.4.2 Effect of online acute stress on executive control

To measure the effect of acute stress on executive function we estimated a mixed effects logistic regression on trial-level log-transformed response times (RTs) on the Stroop task with group, sex and congruency as effect-coded predictors. There was no main effect of group on RT (β_{group}=-0.03, p=0.087) but there was a significant group*sex interaction ($\beta_{group*sex}$= -0.05, p<.001) such that stress was associated with greater speeding of responses in the female compared to male participants (**Figure 2-5**).

We also found the expected speeding effect of congruency on RT (β_{congr}=-0.11, p<.001) but there were no group*congruency (p=0.96) nor group*congruency*sex (p=0.56) interactions indicating that the Stress and Control groups did not differ in the degree of slowing caused by the Incongruent trials. These results suggest that acute stress in female participants more so than in male participants led to an improvement in overall executive control as demonstrated by faster responses across trial types. Regression coefficients are presented in **Supplementary Table 6**.

2.4.3 Relationship between mood, cognition and chronic and life stress measures

We ran two sets of exploratory analyses. In the first, to determine whether the magnitude of the stress-induced mood response was associated with the degree of cognitive performance change,

we examined the relationship between self-reported mood *during* the stress manipulation and task performance. These analyses were conducted only in participants who underwent the stress manipulation. We conducted linear regressions predicting cognitive performance, which reflected either the *change* in performance (in the case of the Corsi performance, which was measured before and after stress) or the post-stress performance (in the case of two-back and Stroop performance), with the change in mood, sex, and their interaction as predictors. There was no relationship between the effect of acute stress on mood and the stress-induced change in cognitive performance (Corsi task, β_{delta_GB}=0.000, β_{sex}=0.046, β_{delta_GB*sex}=-0.000, all p>0.3), nor were there any significant relationships between the effect of acute stress on mood and the post-stress cognitive performance (n-back β_{delta_GB}=0.000, β_{sex}=0.002, β_{delta_GB*sex}=-0.000, Stroop β_{delta_GB}=0.028, β_{sex}=87.079, β_{delta_GB*sex}=-0.087, all p>0.3). There were also no main effects of sex (ps>0.2) and no significant sex*mood_change interactions (ps>0.6). These analyses were also conducted using the Calm-Nervous subscale and the post manipulation and analyses showed a similar pattern. See **Supplementary Tables 7-9** for a summary of the regression coefficients.

In the second set of exploratory analyses, we examined the relationship between our measures of life stress (HR), perceived stress (PSS) and depression (GDS) and degree of stress-induced change in mood. Here too, analyses were conducted only in participants in the Stress group. We ran three separate linear regressions predicting the change in Good-Bad score life stress/perceived stress/depression, sex, and their interaction as predictors. There were no significant relationships between any of the questionnaire scores and the degree of stress-induced mood change (all ps>0.2), nor were there any sex or interaction effects (all ps>0.6). Analyses were also conducted using the Calm-Nervous subscale and the post manipulation stress score with results showing a similar pattern. All regression coefficients can be found in **Supplementary Tables 10-12**.

2.5 Discussion

Acute stress is a ubiquitous feature of everyday life, affecting young and old alike. Though it is generally thought to exert detrimental effects on executive functions, the effects of acute stress on cognitive processing have largely been studied in younger, college-aged populations. In this study we tested the effects of acute stress on working memory and executive control in a large sample

of male and female middle and older-aged participants using a fully remote online stress paradigm. Our findings reveal an overall beneficial effect of stress on cognitive performance, though, notably, the presence of stress-induced improvement varied by sex in a task-dependent manner. More specifically, in the case of spatial working memory, the only cognitive process that was tested both before and after the manipulation, males showed greater improvement than females after stress. In contrast, the benefits of stress on verbal working memory were observed in both men and women and in the case of executive control, greater performance benefits were observed in women than men. Taken together, our results suggest that middle and older aged adults generally experience beneficial rather than detrimental effects of stress on executive functions, which may reflect the ability to recruit additional resources for cognitive processing in a way that is sex dependent.

Previous accounts of stress effects on cognition have proposed that acute stress leads to the reallocation of cognitive resources towards the stressor resulting in impaired cognitive function, and that this effect seems to be especially apparent for cognitive processes, like executive functions, that depend on the prefrontal cortex (Arnsten, 2009). Consistent with this, higher baseline cognitive capacity protects from the detrimental effects of stress on executive functions and other prefrontal cortex dependent tasks (Aranovich et al., 2016; Otto et al., 2013; Quaedflieg et al., 2019). Considering that executive functions like working memory and executive control tend to decline with age (Bopp & Verhaeghen, 2020; Park & Reuter-Lorenz, 2009), it is interesting that we found a global pattern of stress-related improvement rather than impairment in working memory and executive control in this sample of middle and older aged participants. Our results add to the body of literature showing either neutral or beneficial effects of stress across different executive functions in older adults compared to the more commonly reported detrimental effects in younger adults (Dierolf et al., 2018; Pulopulos et al., 2015; Schnitzspahn et al., 2022; Wolf et al., 2001), though a recent meta-analysis highlights the variability of these effects (Mikneviciute et al., 2022). This raises interesting questions about possible mechanisms explaining age differences. One possibility that has been raised is that the subjective and resulting physiological effects of stress are dampened with age; however, a few studies directly comparing younger and older individuals have shown similar patterns of increased cortisol across age groups following an acute stressor (Dierolf et al., 2018; Hidalgo et al., 2015). Another possibility is that younger and

older adults recruit different brain regions in support of executive functioning, and that these regions may be differentially sensitive to stress. For instance, a recent meta-analyses of fMRI studies of working memory function over the lifespan suggested that prefrontal cortex recruitment during the n-back task lessens linearly with increasing age, with changes apparent as early as middle age, and that other regions like the parietal cortex, may display compensatory recruitment (Yaple et al., 2019). Future research will be required to better delineate the mechanisms underlying the differential sensitivity to stress across age groups.

Our findings also emphasize the importance of considering sex differences in research about the effects of acute stress on cognition. As with the effects of age, there are conflicting results in the literature on the effect of sex on stress susceptibility. For example, working memory seems to be more susceptible to stress in young men than in young women, although the direction of this difference is variable across studies (Schoofs et al., 2013; Zandara et al., 2016). Furthermore, in contrast to age, which does not seem to alter cortisol responses to acute stress (Dierolf et al., 2018; Hidalgo et al., 2015), there are some reports of sex differences in cortisol responses (Schoofs et al., 2013; Zandara et al., 2016) though not all studies report consistent findings, and most studies have been conducted in young adults (Almela, Hidalgo, Villada, Espín, et al., 2011; Kudielka & Kirschbaum, 2005; Liu et al., 2017). We found better spatial working memory after stress in men, better executive control performance after stress in women, and better verbal working memory in both men and women after stress. These task-specific effects of sex across different components of executive function were unexpected, but given known intra-individual variability in performance across different executive function tasks, the inconsistent sex differences between tasks may reflect individual differences more broadly (Friedman & Miyake, 2017). It is important to point out another likely source of variability in our study: given the age range of our female participants (43 to 74) and given that the average age of menopause is 45-55 (The North American Menopause Society, 2023), it can be assumed that this sample consisted of peri- and post-menopausal women (and possibly pre-menopausal), in whom differential levels of sex hormones may be differentially affecting stress susceptibility. Indeed, progesterone and estrogen, which are found in higher concentrations in younger women, are thought to blunt the stress response by acting on glucocorticoid receptors and mineralocorticoid receptors, resulting in blunted physiological stress responses and reduced effects of stress on cognition (Kluen, Agorastos, et al.,

2017a, 2017b; Kudielka et al., 1999; Kudielka & Kirschbaum, 2005; Lindheim et al., 1992; Liu et al., 2017). A few studies have suggested that sex differences in stress responses persist with age (Hidalgo et al., 2015; Kudielka & Kirschbaum, 2005), though this is surprising considering the significant age-related reduction in sex hormones that occurs in women as they transition towards the post-menopausal stage (Greendale et al., 1999; McKinlay, 1996). Unfortunately, a weakness of the current study is that we did not control for the menstrual status of women and, because the age of menopause onset is highly variable, it is not possible to deduce it. Future work conducted online or in the laboratory, could include a variety of self-report or physiological measures related to relevant indices of participants' hormonal status to better understand the mechanisms that cause sex, as well as age-dependent differences in the biological and cognitive response to acute stress.

Our study was conducted entirely remotely without interaction with a researcher, incorporating elements from traditional methods of acute stress induction (Almazrouei et al., 2022; Dedovic et al., 2005; Henckens et al., 2009; Levine & Edelstein, 2009; Samide et al., 2020). The online stress induction was successful in that there were significant and substantial differences in the self-reported pre- and post-manipulation mood and stress ratings similar to those observed in other online acute stress inductions. Nonetheless, there are a few limitations when using an online study; the first of which is the potential exclusion of large numbers of participants due to incomplete data and the possibility of data loss, both of which could lead to a potentially biased sample and may affect the generalizability of findings. A second limitation of this study is that we do not have physiologic measures of the stress response to complement the self-report measures. On this point, a few recent studies employing similar online stress induction paradigms additionally validated the methodology against physiological measures of stress such as heart rate variability or cortisol. These studies showed that fully remote online stressors reliably cause changes to physiological measures of stress, and that the magnitude of the stress responses induced online is comparable to the typical stress response elicited in lab (Eagle et al., 2021; Gunnar et al., 2021; Harvie et al., 2021; Meier et al., 2022). For example, typical increases in salivary cortisol following the TSST are around 8 nmol/l (Kudielka et al., 2004), which is similar to the increase observed in online adaptation by Meier and colleagues (2022). Our results therefore also support the feasibility of extending the use of online stress inductions to middle and older aged adults. Taken together, we believe this study provides an important proof-of-principle highlighting the usefulness of fully

online, remote studies (i.e., not requiring interactions with an experimenter) enable the scaling of this sort of stress research to sample sizes that are traditionally not possible with in-lab research. Indeed, the increased power afforded by online research will be important for resolving open questions about the role of sex and other factors likely to play a role in individual differences in stress susceptibility.

In conclusion, our findings suggest that in middle and older aged participants, acute stress is associated with improvements rather than impairments in executive function and that the presence of beneficial effects on cognitive performance differs by sex and by task. These findings lend support the idea that effects of acute stress on cognition may change over the lifespan with beneficial effects for cognition occurring in older adults compared to the more typical detrimental effects observed in younger adults but that there is nonetheless substantial variability even within the single domain of executive function. Our findings also show that larger sample sizes can help uncover sex effects on stress susceptibility, a largely unexplored area which, given the ubiquitous nature of stress, could potentially provide insights more broadly into sex differences in age-related cognitive changes. Finally, our findings demonstrate the viability of fully online and remote acute stress induction procedures. Establishing the feasibility of conducting stress research entirely remotely can provide valuable input for future stress research and, considering the reduced burden to participants in this design, may help reduce barriers for certain populations to participate in research studies, such as people with limited mobility.

Declarations of interest

None

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Authorship contributions

Lyla Hawari: Formal analysis, Writing – Original Draft; **Mario Bogdanov:** Conceptualization, Formal analysis, Writing – Review & Editing; **Léah Suissa-Rocheleau:** Conceptualization**,** Methodology**,** Data Collection; **A. Ross Otto:** Interpretation, Writing – Review & Editing; **Madeleine Sharp:** Conceptualization, Methodology, Writing – Review & Editing, Supervision, Funding Acquisition.

Supplementary Table 1. Effect of acute stress on self-reported mood on the Good-Bad subscale
1A. Three-way ANOVA (group*timepoint*sex) predicting score on the Good-Bad subscale of the Multidimensional Mood Questionnaire as a function of group (stress vs. control), timepoint (pre-manipulation, immediately post-manipulation, end of study) and sex.

Coefficient	***F-value***	***p-value***	
Group	13.663	< **.001**	*
Timepoint	10.648	<**.001**	*
Sex	2.083	0.15	
Group*timepoint	27.417	<**.001**	*
Group*sex	0.601	0.44	
Timepoint*sex	0.628	0.53	
Group*timepoint*sex	0.058	0.94	

1B. Post-hoc t-tests to examine the effects of acute stress on the Good-Bad score

Comparison	***t-value***	***p-value***	
Good-Bad_change (time2-time1) ~ group	-10.36	< **.001**	*
Good-Bad_time2 ~ group	-7.49	< **.001**	*
Good-bad ~timepoint (stress group participants)	7.64	< **.001**	*

Supplementary table 2. Effect of acute stress on self-reported mood on the Calm-Nervous subscale
2A. Three-way ANOVA (group*timepoint*sex) predicting score on the Calm-Nervous subscale of the Multidimensional Mood Questionnaire as a function of group (stress vs. control), timepoint (pre-manipulation, immediately post-manipulation, end of study) and sex.

	F-value	***p-value***	
Group	19.442	< **.001**	*
Timepoint	12.156	<**.001**	*
Sex	1.025	0.312	
Group*timepoint	31.793	<**.001**	*
Group*sex	0.941	0.33	
Timepoint*sex	0.434	0.65	
Group*timepoint*sex	1.201	0.30	

2B. Post-hoc t-tests to examine the effects of acute stress on the Calm-Nervous score

T-test	***t-value***	***p-value***	
Delta: stress-control	-11.1	< **.001**	*
Timepoint 2: stress-control	-8.56	< **.001**	*

Stress: timepoint1-timepoint2	7.80	**< .001**	*

Supplementary Table 3. Effect of acute stress on self-reported stress post manipulation
3A. Linear regression (group*sex) predicting score on the post manipulation stress question as a function of group (stress vs. control) and sex.

	Coefficient estimate	***p-value***	
Group	17.793	**< .001**	*
Sex	-1.627	0.5170	
Group*sex	5.184	**0.0411**	*

Supplementary Table 4. Effect of acute stress on corsi weighted accuracy
4A. Three-way ANOVA (group*timepoint*sex) predicting weighted accuracy score on the corsi block tapping task as a function of group (stress vs. control), timepoint (pre-manipulation, post-manipulation) and sex.

	F-value	***p-value***	
Group	0.073	0.778	
Timepoint	8.259	**0.005**	*
Sex	0.400	0.529	
Group*timepoint	0.578	0.449	
Group*sex	0.379	0.540	
Timepoint*sex	0.070	0.792	
Group*timepoint*sex	1.4.762	**0.032**	*

4B. Post-hoc two-way ANOVA (group*sex) to examine the effects of acute stress on the change in corsi weighted accuracy scores (post-pre) as a function of group (stress vs. control) and sex.

	F-value	***p-value***	
Group	0.334	0.5650	
Sex	0.000	0.9840	
Group*sex	5.378	**0.0228**	*

4C. Post-hoc t-tests to examine the effects of acute stress on the change in corsi weighted accuracy scores (post-pre)

T-test	***t-value***	***p-value***	
Male: delta control-stress	-2.0576	**0.04613**	*
Female: delta control-stress	1.2133	0.2322	

4D. t-tests to examine corsi weighted accuracy performance differences within and between groups

T-test	***t-value***	***p-value***
Female pre: stress-control	1.2157	0.2317
Male pre: stress-control	-1.5594	0.1266
Control pre: male-female	1.8698	0.06905
Stress pre: male-female	-0.86772	0.3907
Female post: stress-control	-0.30065	0.7652
Male post: stress-control	0.86142	0.3943
Control post: male-female	-0.24173	0.8103
Stress post: male-female	0.90895	0.3687

Female stress: pre-post	-0.62377	0.5387	
Female control: pre-post	-2.1225	**0.04716**	*
Male stress: pre-post	-2.9807	**0.007389**	*
Male control: pre-post	0.15313	0.8798	

Supplementary Table 5. Effect of acute stress on two-back accuracy
5A. Trial level mixed effects logistic regression (group* TargetTrial*sex) with TargetTrial as a random slope and userID as a random intercept to predict two-back accuracy score as a function of group (stress vs. control), TargetTrial (target, non-target) and sex.

	Coefficient estimate	***p-value***	
Group	0.172384	**0.039**	*
TargetTrial	-0.589627	**<.001**	*
Sex	0.021460	0.797	
Group*TargetTrial	-0.057145	0.354	
Sex*group	-0.048959	0.557	
Sex*TargetTrial	0.028444	0.644	
Sex*group*TargetTrial	0.005787	0.925	

Supplementary Table 6. Effect of acute stress on Stroop response time
6A. Trial level mixed effects logistic regression (group* congruency*sex) with congruency as a random slope and userID as a random intercept to predict log(RT) as a function of group (stress vs. control), congruency (congruent, incongruent) and sex.

	Coefficient estimate	***p-value***	
Group	-2.977 * 10^-2	0.08712	
Congruency	-1.125 * 10^-1	**<.001**	*
Sex	-8.84 * 10^-3	0.60939	
Group*congruency	2.673 * 10^-4	0.95634	
Sex*group	-4.694 * 10^-2	**0.00752**	*
Sex*congruency	-7.247 * 10^-3	0.13961	
Sex*group*congruency	2.825 * 10^-3	0.56324	

Supplementary Table 7. Relationship between the change in cognitive performance on corsi and the change in mood
7A. Relationship between the corsi change in accuracy score (post-pre) and the change in mood on the Good-Bad subscale (good-bad timepoint 2 – good-bad timepoint 1) interacted with sex. Analysis was repeated using the Calm-Nervous subscale (calm-nervous timepoint 2 – calm-nervous timepoint 1) and the singular post manipulation stress score.

	GBD coeff. (p-value)	CND coeff. (p-value)	SS coeff. (p-value)
questionnaire	0.0001922 (0.307)	0.0001440 (0.482)	-0.0004978 (0.750)
sex	0.04600 (0.625)	-0.0118343 (0.905)	0.1208783 (0.355)
questionnaire*sex	-0.00009976 (0.733)	-0.0003244 (0.306)	-0.0006473 (0.755)

Supplementary Table 8. Relationship between the post-stress cognitive performance on two-back and the change in mood

8A. Relationship between the two-back accuracy score and the change in mood on the Good-Bad subscale (good-bad timepoint 2 – good-bad timepoint 1) interacted with sex. Analysis was repeated using the Calm-Nervous subscale (calm-nervous timepoint 2 – calm-nervous timepoint 1) and the singular post manipulation stress score.

	GBD coeff. (p-value)	CND coeff. (p-value)	SS coeff. (p-value)
questionnaire	0.00007399 (0.352)	1.040*10^-04 (0.213)	-6.765*10^-05 (0.910)
sex	0.001590 (0.969)	-1.823*10^-02 (0.665)	6.955*10^-03 (0.893)
questionnaire*sex	-0.000004189 (0.973)	-6.497*10^-05 (0.619)	-5.542*10^-05 (0.947)

Supplementary Table 9. Relationship between the post-stress cognitive performance (RT) on Stroop and the change in mood

9A. Relationship between Stroop response time and the change in mood on the Good-Bad subscale (good-bad timepoint 2 – good-bad timepoint 1) interacted with sex. Analysis was repeated using the Calm-Nervous subscale (calm-nervous timepoint 2 – calm-nervous timepoint 1) and the singular post manipulation stress score.

	GBD coeff. (p-value)	CND coeff. (p-value)	SS coeff. (p-value)
questionnaire	0.02821 (0.840)	0.06962 (0.632)	-0.9817 (0.351)
sex	87.07876 (0.232)	76.29040 (0.308)	44.9228 (0.623)
questionnaire*sex	-0.08676 (0.699)	-0.12553 (0.596)	1.0375 (0.483)

Supplementary Table 10. Relationship between the change in mood on the Good-Bad subscale and perceived stress scores, depression scores and lifetime stress scores

10A. Relationship between the change in mood on the Good-Bad subscale (good-bad timepoint 2 – good-bad timepoint 1) and perceived stress scores interacted with sex. Analysis was repeated using the depression scores from the geriatric depression scale and the lifetime stress scores from the Holmes-Rahe questionnaire.

	Perceived stress scale coefficient (p-value)	Depression scale coefficient (p-value)	Holmes-Rahe coefficient (p-value)
questionnaire	7.870 (0.201)	-1.505 (0.899)	-0.03510 (0.932)
sex	44.024 (0.705)	-18.493 (0.807)	9.36215 (0.913)
mood_scorequestionnaire*sex	-3.220 (0.719)	7.111 (0.642)	-0.04633 (0.926)

Supplementary Table 11. Relationship between the change in mood on the Calm-Nervous subscale and perceived stress scores, depression scores and lifetime stress scores

11A. Relationship between the change in mood on the Calm-Nervous subscale (good-bad timepoint 2 – good-bad timepoint 1) and perceived stress scores interacted with sex. Analysis was repeated using the depression scores from the geriatric depression scale and the lifetime stress scores from the Holmes-Rahe questionnaire.

	Perceived stress scale coefficient (p-value)	Depression scale coefficient (p-value)	Holmes-Rahe coefficient (p-value)
questionnaire	5.318 (0.363)	-4.137 (0.715)	0.05854 (0.881)
sex	32.923 (0.767)	37.551 (0.603)	57.86882 (0.481)

questionnaire*sex	1.469 (0.863)	3.473 (0.812)	-0.09246 (0.845)

Supplementary Table 12. Relationship between post-manipulation self-reported stress and perceived stress scores, depression scores and lifetime stress scores

12A. Relationship between the post-manipulation self-reported stress and perceived stress scores interacted with sex. Analysis was repeated using the depression scores from the geriatric depression scale and the lifetime stress scores from the Holmes-Rahe questionnaire.

	Perceived stress scale coefficient (p-value)	Depression scale coefficient (p-value)	Holmes-Rahe coefficient (p-value)
questionnaire	0.8629 (0.296)	1.745 (0.263)	0.006137 (0.917)
sex	-20.6249 (0.200)	-10.439 (0.313)	-9.178253 (0.453)
questionnaire*sex	1.4013 (0.253)	1.084 (0.594)	0.030799 (0.665)

3 The Effect of Acute Stress on Physiology and Cognition in Parkinson's Disease Patients

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Key words: acute stress, Parkinson's Disease, cortisol, mood, cognition

3.1 Preface

Chapter 2 investigated the effect of an online acute stress manipulation on a healthy middle aged and older adult sample. The methods used in chapter 2 emphasized the possibility of conducting an acute stress study fully remotely at any time without the need for a researcher present, allowing us to reduce the barriers to accessibility often associated with in-lab experiments. This study also allowed us to expand on the existing stress literature, most of which is centered around young adults, to confirm the directionality of stress effects on cognition in older adults as this would be important for our in-person stress study with our PD sample.

Since there has been no previous literature investigating the effects of acute stress in PD in general and on cognition specifically, the findings from chapter 2 served as additional guidance for our predictions and hypotheses. We chose an in-lab design for the following experiment because often changes in cognition following acute stress are associated with changes in cortisol levels and, unlike in older adults where some literature exists, we have no literature to attest to affective nor physiological stress responses that would be produced in PD patients. However, to have a more direct comparison, we also recruited a sample of healthy older adults (OA) for our in-lab study to investigate any group differences in affective, physiological or cognitive responses to acute stress.

Therefore, in chapter 3, we aimed to investigate, for the first time as far as our knowledge, the acute stress response of PD patients both affectively and physiologically and how they compare to those of our OA group. Secondly, we also hoped to investigate the effect of acute stress on cognition in these two groups, feeling more confident about a beneficial effect of acute stress on OAs due to our findings in chapter 2 but uncertain of the potential stress effects on cognition PDs. These two manuscripts together allow us to better understand the effects of acute stress on aging and patient populations to help us make recommendations regarding stress management to potentially increase quality of life and reduce symptom severity.

3.2 Abstract

Stress, which has varying impacts on health, mood and cognition, is frequently self-reported at high levels in patients with Parkinson's disease (PD). Both anecdotal and scientific reports note that patients self-report high sensitivity to stress. However, whether this sensitivity to stress is due to increased physiological stress reactivity remains unknown. Furthermore, studies have shown that stress is associated with worsening of motor symptoms in PD but stress effects on cognitive symptoms remains understudied. To address this gap, we compared acute stress responses in 51 healthy older adults and 50 PD patients physiologically and affectively and investigated the impact of acute stress on working memory. Utilizing a within-subject design, we measured salivary cortisol, blood pressure and mood before and after an acute stress manipulation, which was induced with the socially evaluated cold-pressor test, and compared the effect of acute stress to a Control condition. We found that healthy older adults and PD patients did not differ in their physiological stress responses but that PD patients showed a blunted affective response to acute stress compared to healthy older adults. We also found that healthy older adults showed a beneficial effect of acute stress on working memory performance, which is consistent with prior research, but PD patients did not show this beneficial effect.

3.3 Introduction

Both clinicians and patients have widely observed that individuals with Parkinson's disease (PD) are highly susceptible to stress (van der Heide, Speckens, et al., 2021). For instance, tremor and freezing of gait, two cardinal motor symptoms of PD, are worsened by stress (Dirkx et al., 2020; van der Heide, Meinders, et al., 2021). Furthermore, recent research in a large patient cohort has shown higher self-reported stress levels in PD patients compared to controls with patients noting stress effects on both motor and cognitive symptoms (van der Heide, Speckens, et al., 2021). Yet, the underlying mechanisms for this stress susceptibility are unknown. Particularly, whether this represents a heightened activation of the physiological stress cascade or whether, instead, this merely represents increased susceptibility of the already impaired motor and cognitive system to cope with stress is unclear. Surprisingly, there have been no studies measuring the physiological effect of acute stress in PD patients under controlled conditions.

Biologically, the stress response consists of two streams: the fast, short-lived response of the autonomic nervous system (ANS), responsible for the secretion of monoamines (e.g. noradrenaline and dopamine) and the slower, more prolonged response of the hypothalamic-pituitary-adrenal (HPA) axis responsible for the secretion of glucocorticoids such as cortisol often referred to as the stress hormone. No study to date has examined the biological stress response in PD patients but there is reason to suspect a dysfunction in the HPA axis following a review of 14 studies, half of which reported elevated baseline cortisol levels in PD patients suggesting a possible mechanism for the worsened symptoms (Soares et al., 2019).

If there exists an abnormal HPA activation to acute stress in PD, it would be plausible to assume that cognition would also be affected. Due to cortisol’s ability to cross the blood-brain barrier, it can affect neural processes across the brain and, consequently, a broad scope of cognitive processes (Francis & Meaney, 1999). Even without an acute stressor, PD patients already show impairments across multiple domains of cognition such as working memory, learning, executive and visuospatial functioning and often continue to develop mild cognitive impairment (Dubois & Pillon, 1996; Hsieh et al., 2008; Marinus et al., 2003; Pigott et al., 2015; Pirogovsky-Turk et al., 2017; Poletti et al., 2012; Timmer et al., 2017). These cognitive deficits could be further

exacerbated by stress, however, there have been no studies that have investigated the effect of acute stress on cognition in PD patients in an experimental setting. In general, the effects of acute stress are heterogeneous depending on the cognitive process and are subject to individual differences such as age and sex. For example, acute stress has been shown to have detrimental effects on cognitive effort and functions such as working memory and response inhibition in young populations, however these effects are often negated or even reversed when exploring these relationships in older adults (Bogdanov et al., 2021; Lupien et al., 2007; Pulopulos et al., 2013; Sandi, 2013; Schnitzspahn et al., 2022; Schoofs et al., 2009; Wolf et al., 2001). Although variable in directionality, the effect of acute stress on cognition is often thought to be associated with changes in cortisol (Bogdanov & Schwabe, 2016; Goldfarb et al., 2017; Shields et al., 2016). Importantly, it is improbable that these differing effects of acute stress result from differing HPA responses since younger and older adults show similar patterns of activation (Hidalgo et al., 2015; Seeman et al., 2001). Acute stress also interacts with other factors such as the development and worsening of prevalent psychiatric disorders like depression and anxiety, which occur frequently across the entire lifespan, especially in aging and patient populations, therefore expecting a uniform effect of acute stress on cognition across populations is unlikely (Bibbey et al., 2013; Grynderup et al., 2013; Puig-Perez et al., 2016; Ryder et al., 2002; Timmer et al., 2017; Young et al., 2000).

Here, we aimed to compare the effects of an acute stress manipulation on self-reported mood, self-reported stress, salivary cortisol levels, motor symptoms and cognitive performance between older adults (OA) and PD patients. Using a within-subject design, participants completed a stress session and a control session in counterbalanced order. The stress manipulation consisted of the widely used socially evaluated cold-pressor test (SE-CPT, Schwabe et al., 2008). Blood pressure, salivary cortisol and mood were measured before and after the manipulation. Working memory was tested before and after the manipulation since this domain is frequently reported to be impacted by both stress and by PD (Marinus et al., 2003; Mikneviciute et al., 2022; Poletti et al., 2012). We hypothesized that PD patients would show greater stress effects both in terms of a greater worsening in self-reported mood and larger stress-related increases in cortisol and blood pressure measures compared to healthy older adults. We also hypothesized that PD patients would show worsening of working memory in relation to acute stress in contrast to the older adults who would

show neutral or beneficial effects of acute stress on working memory, consistent with prior literature (Crosswell et al., 2021; Dirkx et al., 2020; Mikneviciute et al., 2022, 2023; Soares et al., 2019; van der Heide, Meinders, et al., 2021). Given that recurring stress has been linked to worse mental and physical health (DeLongis et al., 1988; McLaughlin et al., 2010; Shields & Slavich, 2017; Toussaint et al., 2016), determining if PD causes a heightened sensitivity to stress could offer insights into the elevated occurrence of psychiatric symptoms and could offer novel therapeutic targets for the management of these symptoms.

3.4 Methods

Participants: Sixty patients with Parkinson's disease (PD) were recruited from the Movement Disorders clinic at the Montreal Neurological Institute and from the Quebec Parkinson's Network (a registry of patients interested in research who have been referred by their neurologist). Fifty-two healthy controls were recruited from spouses and friends of patients and from community groups. Participants were excluded if they had body mass index above 35 or below 17, had significant neurological conditions other than PD (traumatic head injuries, seizures or brain tumors), had current active psychiatric disorders and addiction (including regular use of recreational drugs and smokers), and, in the case of women, had not gone through menopause. We also excluded participants if they were taking the following medications thought to interfere with the stress response: antihistamines, serotonin and norepinephrine reuptake inhibitors (SNRIs) or stimulant drugs and oral corticosteroids. The Montreal Cognitive Assessment (MoCA) was administered at the first visit to exclude participants with a score lower than 24. Ten PD participants were excluded: four were excluded for MoCA < 24, two because of a change in their clinical condition, three were excluded because of medication interference, one was excluded for having another neurological disorder and one was excluded for taking too many medications. One OA participant was excluded for taking SNRIs. The final sample consisted of 51 OA (mean age: 66.6, 43% male) and 50 PD (mean age: 67.4, 54% male) who completed two sessions each, one control and one stress except for four PD participants who withdrew from the experiment after the first session. Data from these withdrawn participants' first sessions was still used in analyses. All participants signed an informed consent form and were compensated 10 CAD/hour for their participation. In keeping with other stress manipulation studies, participants were initially deceived

about the true purpose of the experiment and were told only that this was a study about the effect of emotions on cognition. All participants were fully debriefed at the end of their second session. All procedures were approved by the McGill University Health Centre Research Ethics Board.

Table 3-1: Participant characteristics

	OA (n=51)	**PD (n=50)**	p-value
Age	66.6 (6.62, 55-80)	67.4 (7.75, 52-83)	0.55
Sex (#males/ females)	22/29	27/23	0.20
Education (years)	17.3 (2.92, 11-26)	16.4 (2.41, 12-23)	0.08
Montreal Cognitive Assessment (MoCA)	27.3 (1.91, 24-30)	26.7 (1.98, 24-30)	0.13
Geriatric Depression Scale (GDS)	2.04 (2.83, 0-13)	3.11 (3.48, 0-11)	0.10
Perceived Stress Scale (PSS)	12.8 (7.31, 2-36)	15.2 (5.68, 1-30)	0.08
Holmes-Rahe Life Stress Inventory	117.3 (105.2, 0-575)	162.2 (133.2, 0-587)	0.07
Disease duration	-	8.82 (5.95, 1-27)	-

Values represent mean (SD, range).

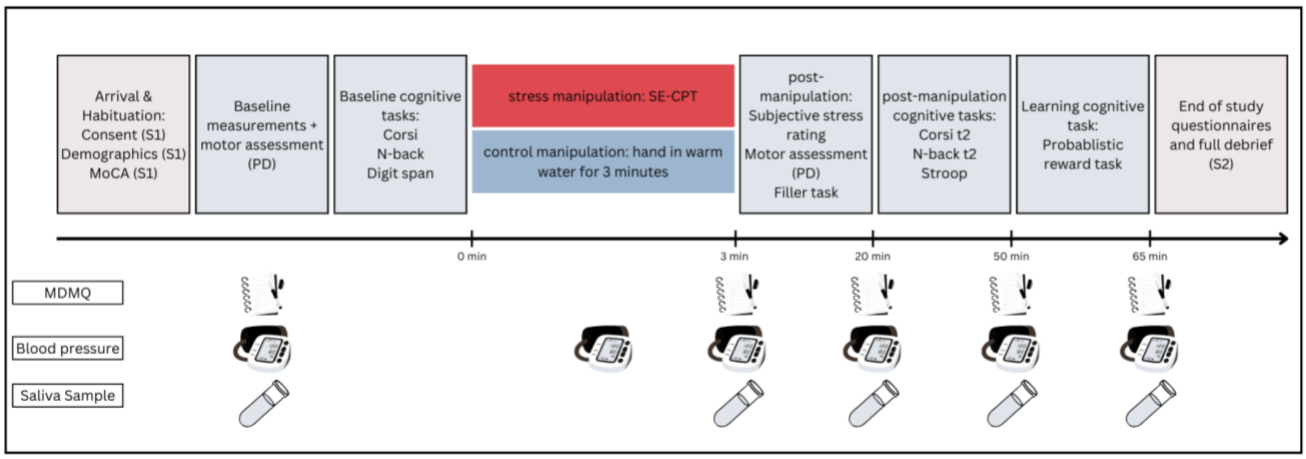

Figure 3-1. Schematic of the experimental procedure and timeline. Participants were randomly assigned to either a stress or control session as their first session then returned to the lab 2-4 weeks later to complete the other condition. The first and last block are session dependent.

Procedure

The procedure is depicted in Figure 3-1. All sessions were run between 2 pm to 6 pm to minimize the effect of diurnal cortisol levels and each participant had their first and second sessions at the same time of day. Participants had the choice for the experiment to be conducted either in English or in French. Each participant came into the lab for two 2-hour sessions that were 2-4 weeks apart. Participants were randomly assigned to either Stress or Control condition on their first session. Participants were given 10 minutes to habituate before starting the experiment. Briefly, self-reported affective measures, blood pressure and salivary cortisol were measured at multiple timepoints: pre-manipulation, immediately post-manipulation, and three additional times over the next 65 minutes, with blood pressure additionally being measured during the manipulation. PD participants also underwent a motor assessment pre- and post-manipulation. Cognitive tasks were also administered both before and after the manipulation. Because we were primarily interested in the possible effects of stress-induced cortisol increases on cognition, and in keeping with other studies of the effects of stress on cognition, post-manipulation cognitive testing started 20 minutes after the initiation of the manipulation, which is when cortisol levels are thought to peak (Schwabe et al., 2008; Schwabe & Schächinger, 2018). While waiting to reach this 20-minute mark participants were given a processing speed task (to be analyzed separately) and were provided with National Geographic magazines to read. Questionnaires assessing depression (Geriatric Depression Scale, GDS; Montorio & Izal, 1996), perceived stress in last month (Perceived Stress

Scale, PSS; Lee, 2012) and lifetime stress (Holmes-Rahe Stress inventory, Noone, 2017) were administered at the end of the second session before the debriefing.

Manipulation

Stress condition: The manipulation used to induce acute stress was the socially evaluated cold-pressor test (SE-CPT, Schwabe et al., 2008). This manipulation induces stress using five main elements: cold stress, uncertainty, continuous evaluation, self-monitoring, lack of social support (Schwabe & Schächinger, 2018). Participants are asked to keep their hand in a tub of ice water (0-4 °C) for as long as possible while watching their own facial expressions through a tablet and being evaluated by a stoic, non-responsive confederate, who is introduced to the participant as a researcher specialized in assessing body language and facial expressions. If participants reach unknown maximum time of 3 minutes, they are instructed by the researcher to remove their hand. Before the manipulation, the primary researcher gives the participant the following instruction on a piece of paper and leaves the room:

"In the following part of the experiment, you are asked to immerse your left hand, including the wrist, into a tank containing ice water. Please keep your hand in the water. The experimenter will let you know when you are allowed to take your hand out of the water. Only if you are not able to tolerate the cold water anymore, you are allowed to take your hand out of the water before you are told to do so by the experimenter. However, please keep your hand in the water for as long as possible, this is important for our study! During the hand immersion, your facial expression will be videotaped. Please look into the camera all the time and please do not speak."

The new stoic researcher enters wearing a lab coat and carrying a clipboard and does not communicate with the participant outside of providing reminders such as "keep your hand fully submerged" or "keep looking into the camera". If participants remove their hand, they are instructed by the researcher to try again. However, if they remove their hand a second time they are instructed to just continue looking into the camera.

Control condition: In the control manipulation, there is no stoic researcher and the primary researcher simply instructs the participant to place their hand in a tub of warm water for 3 minutes without any evaluative elements nor video recordings. The instruction is as follows:

"In the following part of the experiment, you are asked to immerse your left hand, including the wrist, for 3 minutes into a tank containing warm water. The experimenter will let you know when the 3 minutes are over, and you are allowed to take your hand out of the water. This procedure serves as a control manipulation and is experienced as rather neutral by most participants."

Mood measures

For the repeated pre- and post-manipulation mood measurement we used the Good-Bad and Calm-Nervous subscales from the Multidimensional Mood State Questionnaire (Eid et al., 1994; Steyer et al., 1997), consisting of 16 total questions which have shown sensitivity to acute stress (Bogdanov & Schwabe, 2016; Cahlíková & Cingl, 2017; Het & Wolf, 2007). In addition, immediately post- manipulation participants were also asked to rate how stressed they were feeling. This was done only once after the manipulation so as to avoid unveiling the purpose of the study. Responses to all questions were provided using a slider coded from 0-100.

Physiological measures

Blood pressure: systolic and diastolic measurements were taken using a cuff (LotFancy, USA) on the right arm elevated on a table to be roughly at heart level. At each measurement instance, blood pressure was measured twice for accuracy with a 30 second rest interval between the two measures. The first measurement taken during the manipulation began 30 seconds after the start. For analyses, the average of the two systolic measurements per timepoint were used.

Salivary cortisol: Saliva was collected using Sarstedt salivettes (Sarstedt, Germany) (**Figure 1**). To ensure accuracy, participants were instructed not to eat or drink (except water) 1-2 hours before their session. After the session the salivettes were stored at -80° Celsius. Cortisol samples were analyzed using a high sensitivity enzyme immunoassay at the Center for Studies on Human Stress.

Cognitive tasks

Working memory: Verbal working memory was measured with the two-back task (Conway et al., 2005; Kane & Engle, 2002) pre- and post- manipulation as it has been shown to be sensitive to acute stress (Geißler et al., 2023). This task consisted of a series of 70 letters appearing one at a time on screen. Participants were required to identify whether the letter displayed on the screen at the current trial was the same (target trials, 21/70) or different (non-target trials, 49/70) than the letter appearing two trials earlier. Participants had 2000 ms to respond and timed out trials were removed from the data before analysis. For trial level exclusions: trials with response times (RT) 2.5 standard deviations greater or lesser than a participant's average RT were removed resulting in 0-7 trials removed per participant. One OA and 2 PD were additionally completely excluded and one OA had one timepoint of one session excluded due to poor accuracy or incorrect task behavior. The final sample included in the working memory analyses was 50 OA and 48 PD participants.

Motor assessment

Evaluations were conducted for PD participants pre- and post-manipulation. Post-manipulation assessments were not immediately after the manipulation since they took place after the other assessments (Figure 1) using tremor items of part 3 of the Unified Parkinson's Disease Rating Scale (UPDRS). Specifically, participants were assessed for rest, postural and kinetic tremor as well as dyskinesia at two timepoints per session. Motor symptoms were evaluated in a double-blind manner by Dr. Madeleine Sharp, a neurologist at the Montreal Neurological Institute. For analyses, a total motor score was calculated at each timepoint using a composite of the rest, postural, and kinetic tremor scores and an extra point was added for presence of dyskinesia with higher scores indicating worse severity of motor symptoms.

Data Analysis

The self-reported stress levels were analyzed using a mixed-effects ANOVA with condition (control vs. stress) as a within-subject factor and group (OA vs. PD) as a between-subject factor and their interaction. The mood questionnaire and physiological measurements were analyzed in the same manner with the addition of timepoint (1-5 for MDMQ, 1-6 for blood pressure) as a within-subject factor interacted with the other factors. Significant interaction terms are followed

up by appropriate post-hoc comparisons. The two-back task was analyzed on trial-level data using a logistic mixed effects model on trial accuracy with condition (control/stress coded as -1/1), group (OA/PD coded as -1/1), timepoint (pre/post coded as -1/1) and trial type (non-target/target coded as -1/1) and all interactions as fixed effects. Mixed models also included random intercepts for subject and trial-level predictors that varied within subject as random slopes. Motor videos were analyzed using a repeated measures two-way ANOVA with condition (control vs. stress) and timepoint (pre vs. post) as within-subject factors and their interaction. All analyses were performed in R (version 4.1.2) using R Studio (2021.09.1+372) with the lme4 (1.1-30) package and the rstatix (0.7.2) package.

3.5 Results

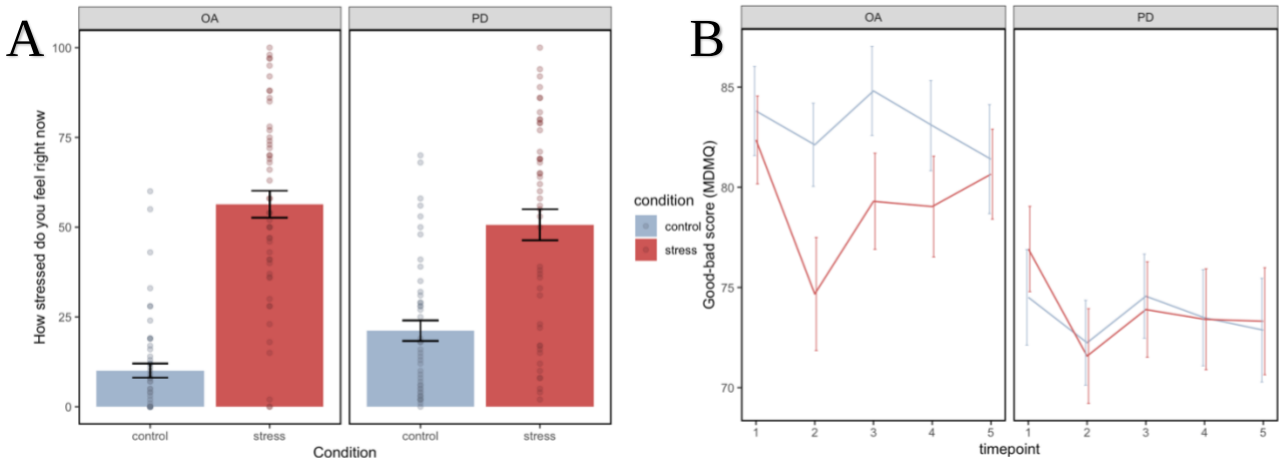

Figure 3-2. The effect of an acute stress manipulation on self-reported mood. A) Scores on the single question that asked "How stressed do you feel right now", presented immediately after the manipulation B) Scores on the Good-Bad subscale of the MDMQ, where a higher score represents better mood, and which were collected at five different timepoints.

3.5.1 Effect of acute stress manipulation on self-reported mood

We first sought to confirm that the stress manipulation was associated with higher levels of stress than the control manipulation and to determine if PD patients and OA differed in the level of self-reported stress. Immediately post- manipulation, participants were asked a single question: "How stressed do you feel right now?". We ran a two-way ANOVA (condition, group, condition*group) on the stress scores and found a significant main effect of condition (F=150, p<.001) on stress

scores and a significant condition*group interaction effect (F=7.12, p=0.009; **Figure 3-2A**). There was no main effect of group (F=0.66, p=0.42). Post-hoc pairwise t-tests revealed significantly higher post-manipulation stress scores in the Stress condition compared to the Control condition in both OA (t=-11.7, p<.001) and PD (t=-6.10, p<.001) groups. There was no significant difference in the post-manipulation stress score between the PD and OA groups in the Stress condition (t=0.95, p=0.344). In contrast, in the Control condition, PD patients reported higher stress levels after the control manipulation than OA (t=-3.15, p=0.002) raising the possibility of higher baseline levels of stress in the PD patients. See **Supplementary tables 1A-C** for all statistical outputs.

Second, we sought to determine if the stress manipulation caused a worsening of mood and whether the PD patients differed from the OA in the degree of their susceptibility to stress based on self-reported mood. We collected self-reported mood using the MDMQ questionnaire at 5 timepoints: pre-manipulation, immediately post- manipulation, and three additional timepoints post-manipulation over a 65-minute period. We used a three-way ANOVA (condition*group*timepoint) and found no significant main effect of condition (F=3.82, p=0.054) but found a significant main effect of timepoint (F=7.94, p<.001), a significant condition*timepoint interaction effect (F=4.23, p=0.004), a significant group*condition interaction (F=5.17, p=0.025; **Figure 3-2B**). We also found a significant main effect of group (F=6.31, p=0.014). First to investigate the condition*timepoint significant interaction, we then ran a one-way ANOVA on timepoint as a post-hoc for each of the Stress and Control conditions separately and found a significant main effect of timepoint in the Stress condition (F=10.7, p<.001) but not in the Control condition (F=2.46, p=0.063). Pairwise post-hoc t-tests showed that for the Stress condition, these differences arose from mood at timepoint 2 being significantly lower than mood at every other timepoint (t_1=5.02, $t_{3\text{-}5}$<-3, all p<.02) whereas for the Control condition none of the timepoints were significantly different. Next, to investigate the significant group*condition interaction, we ran post-hoc t-tests collapsed across timepoints for the OA and PD groups separately. In the OA group, the Stress condition showed significantly lower mood compared to the Control condition (t=5.14, p<.001) whereas for the PD group, there was no difference between the Stress and Control conditions (t=-0.33, p=0.74) collapsed across timepoints. Finally, although the 3-way interaction was nonsignificant, due to our interest in group differences we nonetheless ran a two-way ANOVA for the OA and PD groups separately. In the OA group, found significant

main effects of timepoint (F=4.378, p=0.009) and condition (F=13.7, p<.001) and a significant timepoint*condition interaction (F=4.58, p=0.006) but only found a significant main effect of timepoint (F=3.775, p=0.017) in the PD group. Following up with pairwise post-hoc t-tests, we found that in the OA group, timepoints 1 and 2 were significantly different (t=3.26, p=0.016) whereas in the PD group, none of the timepoints were significantly different. These results suggest that OAs showed the expected worsening of mood on the MDMQ following Stress which was different from their pattern in the Control condition and which matched their self-reported stress levels. However, in PDs, there was no difference in mood pattern between the Stress and Control conditions on the MDMQ even though they did self-report greater stress levels in the Stress condition compared to the Control condition. See **Supplementary tables 2A-G** for all statistical outputs.

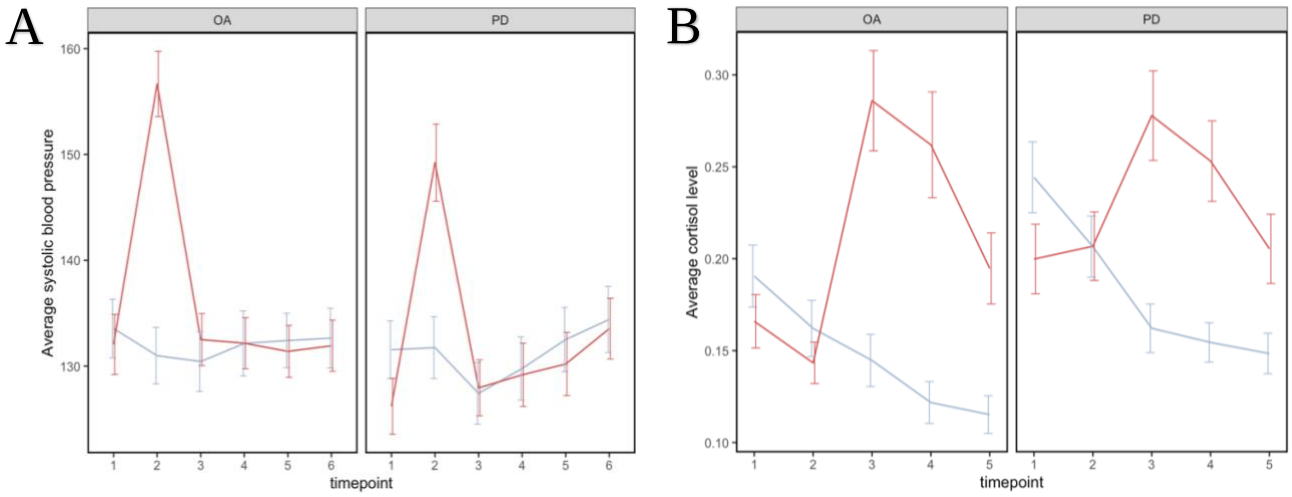

Figure 3-3. The effect of an acute stress manipulation on physiological responses. A) systolic blood pressure and B) Cortisol levels (ug/dl) at multiple timepoints throughout the experiment split by group and condition.

3.5.2 Effect of acute stress manipulation on physiological measures

We collected systolic blood pressure and salivary cortisol measurements at multiple timepoints that matched those of the self-reported mood described above: pre-manipulation, immediately post-manipulation, and three additional measurements over the following 65 minutes. An additional measurement of blood pressure was taken during the manipulation. To analyze the effect of stress on systolic blood pressure, we conducted a three-way ANOVA (condition*group*timepoint) and found a significant main effect of condition (F=5.42, p=0.022)

and a significant condition*timepoint interaction effect (F=58.7, p<.001; **Figure 3-3A**). We also found a significant main effect of timepoint (F=46.8, p<.001) and a significant group*timepoint interaction (F=2.71, p=0.04). First, disregarding groups to verify the effect of the stress manipulation, we ran a one-way ANOVA on timepoint collapsed across groups for each of the Stress and Control conditions separately and found a significant main effect of timepoint in both the Stress (F=75.5, p<.001) and Control (F=4.65, p=0.002) conditions. Pairwise post-hoc t-tests showed that for the Stress condition, this difference arose from measurements at timepoint 2 which were significantly higher than every other timepoint (t_1=-12.8, $t_{3\text{-}6}$>9, all p<.001) whereas for the Control condition only timepoint 3 was significantly different, specifically lower, than timepoints 1, 5 and 6 (t_1=4.13, t_5=-3.83, t_6=-3.71, all p<0.006). Finally, although our 3-way interaction was nonsignificant, due to our interest in group differences we ran a two-way (condition*timepoint) ANOVA on each of the groups separately. In OAs, there was a significant main effect of condition (F=7.89, p=0.007), timepoint (F=34.2, p<.001) and a significant timepoint*condition interaction (F=53.5, p<.001). However, in the PD group, there was no significant main effect of condition, although there was a significant main effect of timepoint (F=18.2, p<.001) and a significant timepoint*condition interaction (F=16.2, p<.001). These results suggest that the OA and PD groups do not differ significantly in their systolic blood pressure response to acute stress. See **Supplementary tables 3A-G** for all statistical outputs.

For our second physiological measure, salivary cortisol, we also conducted a three-way ANOVA (condition*group*timepoint) and found a significant main effect of condition (F=22.2, p<.001), timepoint (F=8.36, p<.001) and a significant condition*timepoint interaction (F=42.7, p<.001, **Figure 3-3B**). There was no significant main effect of group or any significant interactions with group. To follow up on the effect of the manipulation on salivary cortisol disregarding groups, we ran a one-way ANOVA on timepoint for each of the conditions separately and found a significant main effect of timepoint for each of the Stress (F=18.4, p<.001) and Control (F=42.7, p<.001) conditions. Pairwise post-hoc t-tests for the Stress condition showed that these differences stemmed from timepoint 3 measurements being significantly greater than those of timepoints 1, 2 and 5 (t_1=-5.38, t_2=-5.86, t_5=5.44, all p<.001) and timepoint 4 measurements also being significantly greater than those of timepoints 1, 2 and 5 (t_1=-3.71, t_2=-4.32, t_5=6.50, all p<0.005) showing a sustained elevation in cortisol levels after the Stress manipulation. In the Control

condition, measurements all timepoints were significantly different from each other except timepoints 4 and 5 (all $t>3.5$, all $p<.007$) showing a sustained decrease in cortisol levels following the Control manipulation. Finally, in the interest of investigating group differences, we also ran a two-way ANOVA (condition*timepoint) for each group separately and found significant main effects of condition (OA: $F=17.20$, $p<.001$; PD: $F=6.76$, $p=0.013$), timepoint (OA: $F=7.16$, $p=0.001$; PD: $F=3.57$, $p=0.035$) and a condition*timepoint interaction (OA: $F=25.8$, $p<.001$; PD: $F=18.4$, $p<.001$) in both groups. These results suggest that there is no difference in cortisol response to acute stress between OA and PD groups. As an exploratory analysis, we were interested in investigating baseline cortisol differences between the groups so we ran a two-way ANOVA (condition*group) on only the first cortisol measurement and found a significant main effect of group ($F=4.19$, $p=0.044$) with PD showing significantly elevated baselines and a significant main effect of condition ($F=9.73$, $p=0.002$). As one last exploratory analysis, we wanted to see whether there were group differences in cortisol under neutral conditions in the absence of acute stress so we ran a two-way ANOVA (group*timepoint) on only the measurements under the Control condition and found a main effect of group ($F=4.99$, $p=0.028$) with PDs showing an overall elevation in cortisol levels and a main effect of timepoint ($F=42.9$, $p<.001$). Taken together with the blood pressure findings, overall, it seems that PD and OA groups do not differ significantly in their physiological response to acute stress, but baseline cortisol differences may be present. See **Supplementary tables 4A-G** for all statistical outputs.

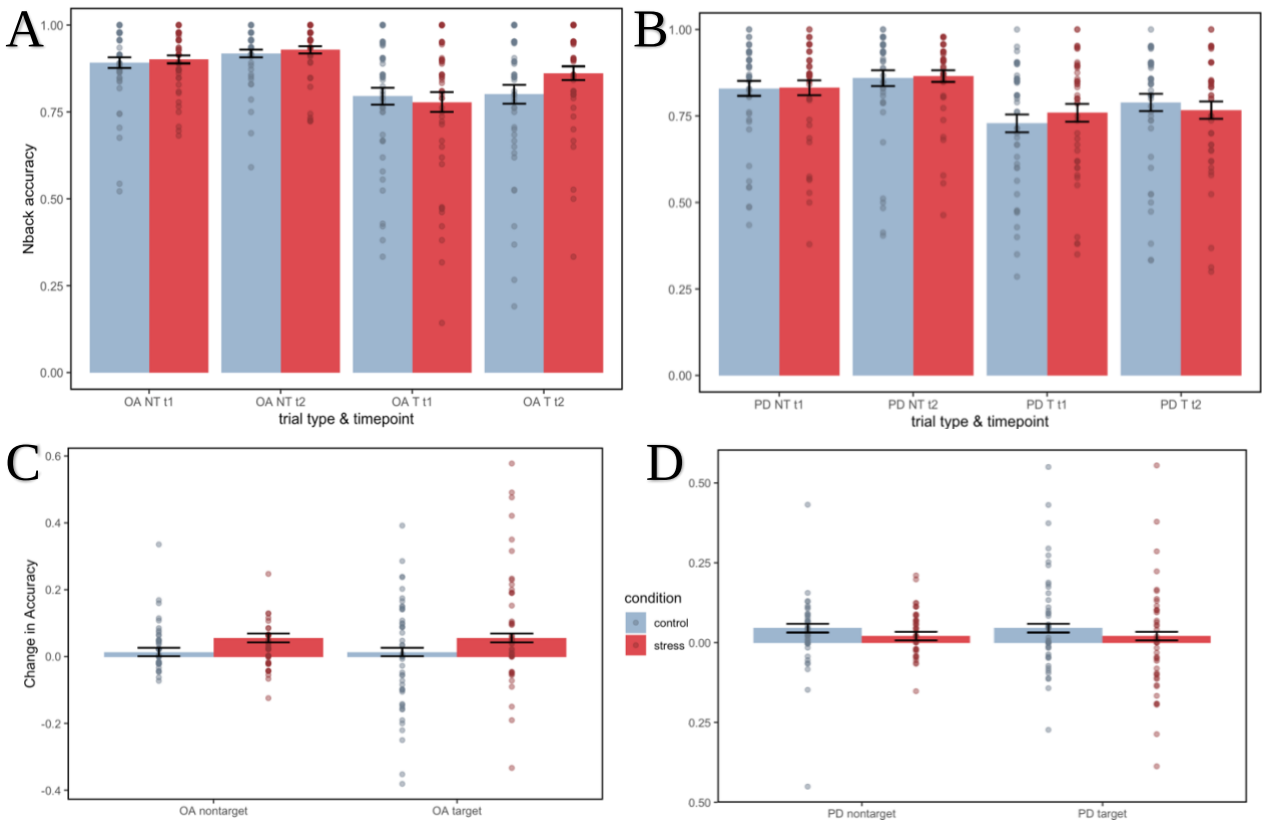

Figure 3-4. The effect of an acute stress manipulation on working memory. Two-back accuracy split by condition, timepoint and trial type for A) OA and B) PD participants separately. C) Change in two-back accuracy (post-pre) split by group, condition, timepoint and trial type.

3.5.3 Effect of acute stress manipulation on working memory

To measure the effect of our acute stress manipulation on working memory, which was measured before and after the manipulation (stress or control), we conducted a logistic mixed effects regression (group*condition*timepoint*trialtype) on the accuracy scores of the two-back task. There was a significant main effect of group showing worse overall accuracy in PD (β_{group}=-0.255, p<.001), and a significant main effect of timepoint showing better performance at timepoint 2 (β_{time}=0.144, p<.001), and trial type showing worse performance on target trials (β_{trial} =-0.402, p<.001) but no significant main effect of condition. There was also a significant group*condition*timepoint interaction ($\beta_{group*condition*time}$=-0.064, p=0.006) and a significant group*condition*timepoint*trialtype interaction ($\beta_{group*condition*time*trial}$=-0.050, p=0.033; **Figure 3-4A-B**). As a follow up, a three-way logistic mixed effects model (group*condition*timepoint) was run on each trial type separately since we were most interested in stress effects on the target trial

performance, as these are the more difficult trials. In the model conducted on target trials, there were again significant main effects of group (β_{group}=-0.192, p=0.033) and timepoint (β_{time}=0.139, p=0.001) and a three-way interaction suggesting that in PD compared to OA, the improvement over time that occurs in the Stress condition is lessened ($\beta_{group*condition*time}$=-0.115, p=0.002). To further tease apart the group differences, we ran logistic mixed effects model on target trial accuracy with condition and timepoint and their interaction as predictors in each group separately. In OA on target trials only, there was no main effect of condition but there was a significant main effect of timepoint (β_{time}=0.173, p=0.011) and a significant condition*timepoint interaction ($\beta_{condition*time}$=0.151, p=0.008) indicating greater improvement in performance after the manipulation in the Stress compared to the Control condition. In contrast, in PD participants, there was only a significant main effect of timepoint (β_{time}=0.106, p=0.049) consistent with practice effects, but, unlike what was observed in the OA, no additional beneficial effects resulting from the stress manipulation. See **Supplementary tables 5A-E** for logistic mixed effects model outputs and coefficient statistics. Overall, these results indicate that acute stress has beneficial effects on working memory in OA but not in PD participants.

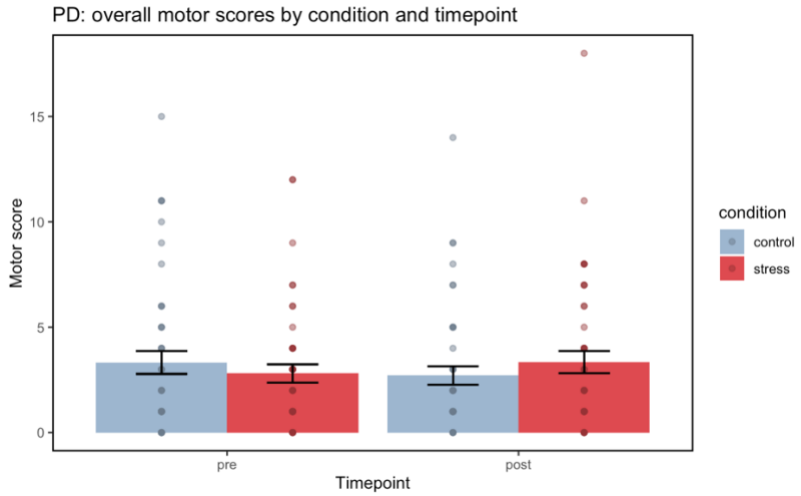

Figure 3-5. The effect of an acute stress manipulation on motor symptoms.

3.5.4 Effect of acute stress manipulation on motor symptoms

To measure the effect of our acute stress manipulation on motor symptoms, which were measured in PD participants before and after the manipulation, we conducted a 2-way repeated measures ANOVA (condition*timepoint). We found no significant main effect of condition or timepoint nor

a significant interaction effect (all $F<2.6$, all $p>0.1$) on overall motor scores. These results suggest that although affected physiologically in terms of cortisol and blood pressure, PD participants did not show a detectable physiological effect of acute stress on motor symptoms.

3.6 Discussion

Acute stress is a universal experience which is further complexified when interacted with a neurodegenerative disease such as PD. Patients anecdotally report greater stress levels and worsening of symptoms under stress so in this study we sought out to investigate whether these differences represent effects of the disease on the physiological stress response. To do so, we compared the effect of acute stress salivary cortisol and blood pressure between healthy older adults (OA) and Parkinson's disease (PD) patients and additionally measured changes in mood and cognitive performance. First, we confirmed that the stress manipulation was effective in both PD and HC: both groups reported significantly higher stress levels in the Stress compared to the Control condition. Second, and contrary to our prediction, we found that both groups showed a significant increase in salivary cortisol and blood pressure after the stress manipulation and that the magnitude of this physiologic stress response was not greater in the PD compared to the older adults. Interestingly, however, despite similar physiologic responses, the older adults showed greater effects of stress on mood than the PD patients. Contrary to our expectations, we did not find an effect of acute stress on motor symptoms. Finally, with respect to the effects of acute stress on cognition, we found that though older adults benefitted from acute stress with an improvement in working memory, the PD patients did not show such benefit. Our findings demonstrate a similarity between OA and PD in the physiological response to acute stress, suggesting normal HPA responsiveness in PD, but a difference in stress-induced cognitive benefits or lack thereof.

We had hypothesized that PD participants would be more sensitive to acute stress than OAs but our results suggest the opposite with PD participants being not as affectively impacted as OA participants in response to acute stress. We had two measures of affect, the single self- reported stress question, and the repeating MDMQ. Looking at self-reported stress, in OAs, we see the expected difference in stress score by around 40 units perfectly aligning with prior literature (Schwabe et al., 2008; Schwabe & Schächinger, 2018). In PDs, although the manipulation had its

intended effect in the Stress condition, we also observed elevated stress levels in the Control condition. These heightened stress levels in the Control condition are supported by literature suggesting that PD patients self-report higher levels of stress compared to healthy older adults (van der Heide, Meinders, et al., 2021; van der Heide, Speckens, et al., 2021) which seems to be the case under neutral conditions (ie in the Control condition), not when exposed to an acute stress, where PD and OA participants self-reported similar stress levels. Looking at our other affective measure, MDMQ ratings, once again OA showed the expected pattern, where participants reported worsening of mood following the stress manipulation but not the control manipulation. Contrarily, in PDs, we found an overall worse mood compared to OAs that was not significantly affected by the condition (stress vs control). To explain this, we look towards other symptoms of PD that may be interacting with this stress response. In addition to depression, anxiety and apathy, PD has also been associated with emotional processing impairments (Péron et al., 2012) with some studies showing that PD patients often exhibit blunted emotional responses, especially to negative or aversive stimuli (Bowers et al., 2006; Dietz et al., 2013; Miller et al., 2009; Wieser et al., 2006). Although the exact mechanism of this emotional blunting remains unknown, it is believed to pertain to dysfunction in the limbic system and we hypothesize that it could be a potential explanation for the lack of an effect of acute stress on mood as reported by MDMQ.

We had hypothesized that PD participants might be more physiologically responsive to acute stress than OAs but our results show a similar pattern in blood pressure and cortisol responses across the two groups. Similar to the affective response, OAs also showed the expected increase in salivary cortisol and blood pressure following stress (Schwabe et al., 2008; Schwabe & Schächinger, 2018) and PDs showed a very similar pattern except for elevation in baseline salivary cortisol levels. This is not uncommon and is thought to be attributed to chronic stress in PD, although some believe it could also be attributed to dopaminergic medications, which are often used to treat PD, having an excitatory effect on the HPA axis (Marakaki et al., 2015; Soares et al., 2019). However, worth noting is the fact that the peak cortisol levels for both OA and PD seem to be lower than those of other studies which reported similar or even stronger cortisol responses to stress in OA compared to younger adults (Almela, Hidalgo, Villada, van der Meij, et al., 2011; Otte et al., 2005). That being said, our peak cortisol levels do seem to align with other studies investigating stress effects in younger and older adults, especially when taking into account the peak levels in the afternoon

since our experiment was conducted in the afternoon (Kudielka et al., 2004; Pulopulos et al., 2013). These deviations in peak cortisol levels could also be a result of our OA sample not being completely equally split between the two sexes, as sex effects on cortisol response have been observed especially in aging populations (Otte et al., 2005; Seeman et al., 2001). Overall, it seems that when discussing differences in response to acute stress, PDs showed a blunted affective response compared to OAs but still demonstrated a comparable physiological response. These initial findings suggest that there may not be detectable differences in the sympathetic nervous system and HPA functioning in PD as demonstrated by blood pressure and cortisol level reactions to acute stress.

In terms of cognition, we hypothesized that acute stress would have positive beneficial on working memory in OA and detrimental effects on PD participants, which was partially supported by our data since OA improved following stress and PD participants showed no change in cognition. In terms of cognition in OA, we observed a clear beneficial effect of stress on our working memory task which aligns with previous literature in OA suggesting null to beneficial effects (Mikneviciute et al., 2022; Pulopulos et al., 2015; Schnitzspahn et al., 2022; Wolf et al., 2001). In contrast, we did not find any significant effects of acute stress on cognition in PD, although we had hypothesized that since acute stress was associated with a self-reported worsening in motor and cognitive symptoms (Dirkx et al., 2020; Soares et al., 2019; van der Heide, Meinders, et al., 2021), it would be detrimental to working memory. However, at this time these results are difficult to interpret since there is no literature surrounding this topic as no study to date has investigated a causal effect of acute stress on PD in a lab environment with regards to either motor or cognitive symptoms. Perhaps the absence of an effect is due to the choice of task and that there may be a more appropriate task to investigate these effects of acute stress on working memory in PD. Being the first of its kind, this study paves the way for future investigations of stress effects on cognition in PD both in working memory and across other executive functions as well.

Given the previous reports of worsening motor symptoms due to stress, we also measured motor symptoms before and after stress in the PD patients. Our examination focused on tremor since this is one of the more quantifiable motor symptoms and one that patients often report being quite sensitive to stress. Although we had hypothesized an exacerbation of motor symptoms following

acute stress, our findings did not support that as we saw no significant change in motor symptoms after the stress manipulation. Previous literature often mentions self-reported worsening of motor symptoms in PD patients when under stress, although none of these studies investigated this under controlled, experimental conditions (Dirkx et al., 2020; Raethjen et al., 2008; Soares et al., 2019; van der Heide, Meinders, et al., 2021; Zach et al., 2017). We did not see a significant difference in motor symptoms pre- vs post- manipulation following the acute stressor but this could partly be explained by the generally lower symptom burden in our patient population, as is often the case for in-lab studies. Another important possibility is that the motor symptoms, which were tested roughly 10 minutes after the stressor, might have been tested too late. Of the few studies that have looked at the association between cortisol and motor symptoms, some found this association although the directionality is unclear, and others did not (Soares et al., 2019). Perhaps, instead, the worsening motor symptoms from stress is related to the faster adrenergic response as opposed to the cortisol response, which peaks around 20 minutes after the stress. Previous studies that have observed increased motor symptoms during periods of high stress (e.g. during cognitively difficult tasks), have observed this increase during the stressful event (Dirkx et al., 2020; Raethjen et al., 2008; Zach et al., 2017).

This study shows that OA and PD are similar in their physiological response to stress, but not their affective response nor the downstream effect on cognition although literature often attributes the stress-related cognitive changes to an increase in cortisol (Bogdanov & Schwabe, 2016; Goldfarb et al., 2017; Shields et al., 2016). OA and PD participants showing similar cortisol increases yet different cognitive stress effects raise the question of a possible difference in stress to cognition mechanism between them. One possible explanation is that PDs have chronically elevated cortisol levels (Soares et al., 2019), observed in our sample, and, to protect from their damaging effects, the brain has downregulated its sensitivity to cortisol, a mechanism seen both in animal and human models (de Kloet et al., 2005; Hinkelmann et al., 2009; Opinion et al., 2023; Rich & Romero, 2005; Shrimpton & Randall, 1994). Specifically, cortisol is thought to downregulate glucocorticoid receptors and mineralocorticoid receptors which are found in prefrontal cortex and hippocampus, brain regions crucial for executive functioning (de Kloet et al., 2005). It is also worth noting that the prefrontal cortex has shown a vulnerability towards chronically elevated cortisol levels (Wellman, 2001). Considering this information, chronic elevations in cortisol levels

could be downregulating the brain's sensitivity to cortisol, and therefore downregulating the beneficial effects of acute stress on cognition in PD patients that occur in healthy older adults.

Our results not only add new information into the small pool of stress literature for older adults but more importantly provide novel insights into the effect of acute stress on PD which, to our knowledge, has never been investigated. Using a large sample size and a within-subject design allowed us to minimize the potential effects of individual differences on our findings. Being the first study of its kind to investigate the effects of acute stress on PD in a lab setting, we thought it essential to collect measures spanning across both affective and physiological responses to give us a more complete first picture of the potential mechanisms and differences between OA and PD participants. Although the literature on stress and PD is sparse at best, we are confident in this study as our first contribution to investigating this topic in an experimental fashion. Moving forward, we hope to investigate stress-induced changes in other physiological markers beyond the HPA axis to tease apart the effects of biological stress on cognition in PD while also examining other cognitive functions that are known to be susceptible to stress.

In conclusion, our findings suggest that OA and PD participants had similar physiological responses but differing affective responses to acute stress and that OAs experienced a beneficial stress effect on working memory which was not seen in PD. These findings lend support to the idea of normal HPA responsiveness in PD to acute stress specifically but not necessarily at baseline and highlight impairments in emotional processing that have been attributed to altered activity in the limbic system. Our findings also emphasize the difficulty in teasing apart the different non-motor symptoms of PD and their potential interactions when studying the effects of acute stress. Finally, our findings delve into unchartered waters by being the first to investigate the effect of acute stress on cognition in PD. Even within the stress literature, previous studies looking at the HPA axis in PD had never observed salivary cortisol changes due to a stress manipulation. Furthering our understanding of the non-motor symptoms of PD and what factors exacerbate them can provide valuable inputs into future disease management plans, potentially focusing on reducing stress levels to improve quality of life.

Declarations of interest

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Supplementary Table 1. Effect of acute stress on self-reported stress ratings
1A. Two-way ANOVA (group*condition) predicting self-reported stress scores as a function of group (OA, PD) and condition (stress, control).

	F-value	***p-value***	
group	0.656	0.420	
condition	149.984	**<.001**	*****
group*condition	7.118	0.009	*****

1B. Post-hoc t-tests to examine the effects of condition on stress score in groups separately

Comparison	***t-value***	***p-value***	
OA: Stress score ~ condition	-11.7	< **.001**	*****
PD: Stress score ~ condition	-6.10	< **.001**	*****

1C. Post-hoc t-tests to examine the effects of condition on stress score in conditions separately

Comparison	***t-value***	***p-value***	
Control: Stress score ~ group	-3.15	**0.002**	*****
Stress: Stress score ~ group	0.945	0.347	

Supplementary Table 2. Effect of acute stress on self-reported mood (MDMQ)
2A. Three-way ANOVA (group*condition*timepoint) predicting good-bad score on the MDMQ as a function of group (OA, PD), condition (stress, control) and timepoint (1-5).

	F-value	***p-value***	
group	6.306	**0.014**	*****
condition	3.823	0.054	
timepoint	7.938	< **.001**	*****
Group*condition	5.174	**0.025**	*****
Group*timepoint	0.271	0.831	
Condition*timepoint	4.233	**0.004**	*****
Group*condition*timepoint	1.168	0.324	

2B. Stress condition: post-hoc one-way ANOVA to examine the effects of acute stress on self-reported mood as a function of timepoint (1-5).

	F-value	***p-value***

Timepoint	10.691	**< .001**	*****

2C. Stress condition: post-hoc paired t-tests to examine the effects of acute stress on the self-reported mood across timepoints

Time1	Time2	***t-value***	***p-value***	
1	2	5.021488	**< .001**	*****
1	3	2.768916	0.068	
1	4	2.794149	0.064	
1	5	2.247359	0.271	
2	3	-3.90477	**0.002**	*****
2	4	-3.20047	**0.019**	*****
2	5	-3.47495	**0.008**	*****
3	4	0.54597	1	
3	5	-0.53666	1	
4	5	-1.1443	1	

2D. Control condition: post-hoc one-way ANOVA to examine the effects of acute stress on self-reported mood as a function of timepoint (1-5).

	F-value	***p-value***
Timepoint	2.458	0.063

2E. Control condition: post-hoc paired t-tests to examine the effects of acute stress on the self-reported mood across timepoints

Time1	Time2	***t-value***	***p-value***
1	2	1.891543	0.618
1	3	-0.55531	1
1	4	0.914897	1
1	5	1.419523	1
2	3	-2.82691	0.058
2	4	-1.26949	1
2	5	0.044005	1
3	4	1.918907	0.582
3	5	2.230871	0.282
4	5	1.17528	1

2F. OA: Two-way ANOVA (condition*timepoint) predicting good-bad score on the MDMQ as a function of condition (stress, control) and timepoint (1-5).

	F-value	***p-value***	
condition	13.698	**< .001**	*
timepoint	4.378	**0.009**	*****
condition*timepoint	4.58	**0.006**	*****

2G. PD: Two-way ANOVA (condition*timepoint) predicting good-bad score on the MDMQ as a function of condition (stress, control) and timepoint (1-5).

	F-value	***p-value***	
condition	0.037	0.847	
timepoint	3.775	**0.017**	*
condition*timepoint	0.908	0.44	

Supplementary Table 3. Effect of acute stress on systolic blood pressure

3A. Three-way ANOVA (group*condition*timepoint) predicting systolic blood pressure as a function of group (OA, PD), condition (stress, control) and timepoint (1-6).

	F-value	***p-value***	
group	0.370	0.545	
condition	5.422	**0.022**	*
timepoint	46.765	< **.001**	*
Group*condition	1.192	0.278	
Group*timepoint	281.53	**0.040**	*
Condition*timepoint	58.734	< **.001**	*
Group*condition*timepoint	1.537	0.199	

3B. Stress condition: post-hoc one-way ANOVA to examine the effects of acute stress on systolic blood pressure as a function of timepoint (1-6).

	F-value	***p-value***	
Timepoint	75.521	< **.001**	*

3C. Stress condition: post-hoc paired t-tests to examine the effects of acute stress on systolic blood pressure across timepoints

Time1	Time2	***t-value***	***p-value***	
1	2	-12.8	< **.001**	*
1	3	-0.898	1	
1	4	-1.06	1	
1	5	-1.20	1	
1	6	-2.38	0.292	
2	3	13.2	< **.001**	*
2	4	10.5	< **.001**	*
2	5	10.8	< **.001**	*
2	6	9.15	< **.001**	*
3	4	-0.307	1	
3	5	-0.386	1	
3	6	-1.69	1	
4	5	-0.0491	1	
4	6	-1.73	1	
5	6	-1.81	1	

3D. Control condition: post-hoc one-way ANOVA to examine the effects of acute stress on systolic blood pressure as a function of timepoint (1-6).

	F-value	*p-value*	
Timepoint	4.65	**0.002**	*

3E. Control condition: post-hoc paired t-tests to examine the effects of acute stress on systolic blood pressure across timepoints

Time1	Time2	*t-value*	*p-value*	
1	2	1.41	1	
1	3	4.13	**0.001**	*
1	4	1.47	1	
1	5	0.156	1	
1	6	-0.625	1	
2	3	2.87	0.078	
2	4	0.278	1	
2	5	-1.28	1	
2	6	-1.90	0.907	
3	4	-2.15	0.519	
3	5	-3.83	**0.004**	*
3	6	-3.71	**0.005**	*
4	5	-1.50	1	
4	6	-2.22	0.44	
5	6	-1.24	1	

3F. OA: Two-way ANOVA (condition*timepoint) predicting systolic blood pressure as a function of condition (stress, control) and timepoint (1-6).

	F-value	*p-value*	
condition	7.888	**0.007**	*
timepoint	34.202	< **.001**	*
condition*timepoint	53.454	< **.001**	*

3G. PD: Two-way ANOVA (condition*timepoint) predicting systolic blood pressure as a function of condition (stress, control) and timepoint (1-6).

	F-value	*p-value*	
condition	0.576	0.452	
timepoint	18.210	< **.001**	*
condition*timepoint	16.177	< **.001**	*

Supplementary Table 4. Effect of acute stress on salivary cortisol

4A. Three-way ANOVA (group*condition*timepoint) predicting good-bad score on salivary cortisol as a function of group (OA, PD), condition (stress, control) and timepoint (1-5).

	F-value	*p-value*	
group	2.839	0.096	
condition	22.171	< **.001**	*
timepoint	8.361	< **.001**	*
Group*condition	0.615	0.435	

Group*timepoint	2.317	0.102	
Condition*timepoint	42.742	< **.001**	*
Group*condition*timepoint	0.980	0.388	

4B. Stress condition: post-hoc one-way ANOVA to examine the effects of acute stress on salivary cortisol as a function of timepoint (1-5).

	F-value	***p-value***	
Timepoint	18.397	< **.001**	*

4C. Stress condition: post-hoc paired t-tests to examine the effects of acute stress on salivary cortisol across timepoints

Time1	Time2	***t-value***	***p-value***	
1	2	1.07	1	
1	3	-5.38	< **.001**	*
1	4	-3.71	**0.004**	*
1	5	-1.11	1	
2	3	-5.86	< **.001**	*
2	4	-4.32	< **.001**	*
2	5	-1.77	0.8	
3	4	1.68	0.966	
3	5	5.44	< **.001**	*
4	5	6.50	< **.001**	*

4D. Control condition: post-hoc one-way ANOVA to examine the effects of acute stress on salivary cortisol as a function of timepoint (1-5).

	F-value	***p-value***	
Timepoint	42.666	< **.001**	*

4E. Control condition: post-hoc paired t-tests to examine the effects of acute stress on salivary cortisol across timepoints

Time1	Time2	***t-value***	***p-value***	
1	2	5.43	< **.001**	*
1	3	6.00	< **.001**	*
1	4	7.57	< **.001**	*
1	5	7.94	< **.001**	*
2	3	4.13	< **.001**	*
2	4	6.00	< **.001**	*
2	5	6.47	< **.001**	*
3	4	3.57	**0.006**	*
3	5	4.36	< **.001**	*
4	5	1.50	1	

4F. OA: Two-way ANOVA (condition*timepoint) predicting good-bad score on salivary cortisol as a function of condition (stress, control) and timepoint (1-5).

	F-value	***p-value***	
condition	17.196	< **.001**	*
timepoint	7.156	**0.001**	*****
condition*timepoint	25.761	< **.001**	*****

4G. PD: Two-way ANOVA (condition*timepoint) predicting good-bad score on salivary cortisol as a function of condition (stress, control) and timepoint (1-5).

	F-value	***p-value***	
condition	6.755	**0.035**	*****
timepoint	3.574	**0.013**	*****
condition*timepoint	18.361	< **.001**	*****

Supplementary Table 5. Effect of acute stress on two-back accuracy

5A. Trial level mixed effects logistic regression (group*condition*timepoint*trialtype) with condition*timepoint*trialtype as a random slope and userID as a random intercept to predict two-back accuracy score as a function of group (OA, PD), condition (stress vs. control), timepoint (pre, post) and trial type (target, non-target).

	Coefficient estimate	***p-value***	
Group	-3.374	**<.001**	*****
Condition	1.341	0.17978	
Timepoint	5.303	**<.001**	*****
Trialtype	-7.955	**<.001**	*****
Group*condition	-1.065	0.28671	
Group*timepoint	-0.721	0.47086	
Condition*timepoint	0.978	0.32814	
Group*trialtype	1.311	0.18969	
Condition*trialtype	0.381	0.703	
Timepoint*trialtype	-0.254	0.780	
Group*condition*timepoint	-2.734	**0.006**	*****
Group*condition*trialtype	-0.017	0.986	
Group*timepoint*trialtype	-0.346	0.729	
Condition*timepoint*trialtype	0.648	0.517	
Group*condition*timepoint*trialtype	-2.132	**0.033**	*****

5B. Target trials only: trial level mixed effects logistic regression (group*condition*timepoint) with condition*timepoint as a random slope and userID as a random intercept to predict two-back accuracy score as a function of group (OA, PD), condition (stress vs. control) and timepoint (pre, post).

	Coefficient estimate	***p-value***	
Group	-2.13	**0.033**	*****
Condition	1.25	0.210	
Timepoint	3.26	**0.001**	*****
Group*condition	-0.769	0.442	
Group*timepoint	-0.730	0.466	

Condition*timepoint	0.982	0.326	
Group*condition*timepoint	-3.15	**0.002**	*

5C. Non-target trials only: trial level mixed effects logistic regression (group*condition*timepoint) with condition*timepoint as a random slope and userID as a random intercept to predict two-back accuracy score as a function of group (OA, PD), condition (stress vs. control) and timepoint (pre, post).

	Coefficient estimate	***p-value***	
Group	-3.51	**<.001**	*
Condition	0.776	0.438	
Timepoint	5.38	**0.001**	*
Group*condition	-0.815	0.415	
Group*timepoint	-0.671	0.502	
Condition*timepoint	0.278	0.781	
Group*condition*timepoint	-0.397	0.691	

5D. OA, target trials only: trial level mixed effects logistic regression (condition*timepoint) with condition*timepoint as a random slope and userID as a random intercept to predict two-back accuracy score as a function of condition (stress vs. control) and timepoint (pre, post).

	Coefficient estimate	***p-value***	
Condition	1.29	0.197	
Timepoint	2.54	**0.011**	*
Condition*timepoint	2.67	**0.008**	*

5E. PD, target trials only: trial level mixed effects logistic regression (condition*timepoint) with condition*timepoint as a random slope and userID as a random intercept to predict two-back accuracy score as a function of condition (stress vs. control) and timepoint (pre, post).

	Coefficient estimate	***p-value***	
Condition	0.461	0.645	
Timepoint	1.97	**0.0486**	*
Condition*timepoint	-1.56	0.118	

4 General discussion

4.1 Overview

In exploring the intricate relationship between acute stress, physiology, and cognition, this thesis presented two distinct studies offering complementary perspectives, collectively shedding light on the nuanced stress responses of both older adults (OAs) and Parkinson's Disease (PD) patients. While the first study delves into the effects of acute stress on a broad spectrum of participants in middle and older age groups, the second study specifically examines the impact on PD patients, a population known to face unique challenges in stress-related responses. By juxtaposing these studies, we aim to clarify the commonalities and disparities in how acute stress influences affective states, physiological markers, and cognitive functions in these two distinct populations. Therefore, in this discussion I aim to 1. compare the findings of the two studies, 2. introduce possible explanations and mechanisms for the group differences observed, 3. suggest future directions that could help further clarify these differences and finally 4. Reiterate the impact and significance of these two papers on the studies populations.

4.2 Acute stress and cognition across older adults and PD patients

Both studies investigated the affective responses to acute stress, revealing intriguing differences between PD patients and OAs. In the chapter 2 and chapter 3, acute stress generally led to mood worsening in middle aged and older adults, in contrast, PD patients demonstrated a blunted affective response to stress, suggesting less sensitivity to acute stress compared to OAs. These seemingly contradictory findings prompt a closer examination of the emotional processing impairments associated with PD. While OAs experienced the expected increase in stress levels following an acute stressor, PD patients demonstrated elevated stress even in neutral conditions. The blunted affective response in PD, as evidenced by both self-report measures and the Mood Disorder Questionnaire (MDMQ), suggests a complex interplay between PD symptoms and stress reactivity.

Unlike chapter 2 which only measured acute stress responses through changes in affect, chapter 3 additionally included physiological responses in the form of blood pressure and salivary cortisol levels. In chapter 3, surprisingly, despite the group differences in affective response, the physiological responses to acute stress appeared similar between PD patients and OAs with both

groups exhibiting the expected patterns of increased cortisol and blood pressure following the stress manipulation. This shared physiological response challenges the initial hypothesis that PD patients might show heightened physiological reactivity to stress. However, the one observed difference in physiological responses was the elevated cortisol levels seen in PDs across both conditions and across timepoints. This raises questions about chronically elevated cortisol levels and a potential downregulation mechanism in PD. Existing published studies collectively suggest that, at least in the context of acute stress, the sympathetic nervous system and HPA axis functioning may not significantly differ between PD patients and OAs.

Cognitive responses to acute stress emerged as a crucial point of divergence between the two studies. Despite the heterogeneity in literature, the beneficial effects of acute stress on executive function that were observed using an online stress manipulation in chapter 2 were replicated with our in-person stress manipulation in chapter 3 with improvements in working memory observed. In contrast, as observed in chapter 3, working memory performance in PD patients did not improve following acute stress despite showing similar physiological responses. These contrasting cognitive responses highlight the complexity of stress effects on cognition in different populations. The next section will be dedicated to the introduction of possible explanations and mechanisms for these differential effects of stress on cognition.

4.3 Possible mechanisms

After comparing the findings of chapters 2 and 3 we can see that there are some differences in acute stress response between OAs and PDs, for which I would like to suggest some possible explanations and potential mechanisms. As outlined in chapter 1, the presence of an inverted u-shaped effect of stress on cognition has been observed in multiple studies and this effect is thought to be attributed to changes in cortisol (Domes et al., 2005; Mateo, 2008; Salehi et al., 2010; Schilling et al., 2013). Referring to the findings in chapter 3, although PDs start at a slightly elevated cortisol level, following acute stress, OAs and PDs are around the same cortisol levels at peak, however this increase in cortisol for OAs is associated with increased cognitive performance whereas for PDs it is not. Assuming the u-shaped curve association between cortisol and cognition, a possible hypothesis for this difference could be that the shape of this curve differs in OAs and PDs. In OAs, the increase in cortisol brings them towards their peak performance levels. In PDs

meanwhile, it is possible that the dynamic range of cortisol is narrower, such that a similar absolute increase in cortisol could cause them to pass the peak performance and land on the downward portion of the curve (**Figure 12-1**). A narrowed curve would imply that there is a very small range of cortisol values that would lead to an improvement, and that any small changes in cortisol levels would have an amplified effect on performance as indicated by the greater distance travelled around the curve.

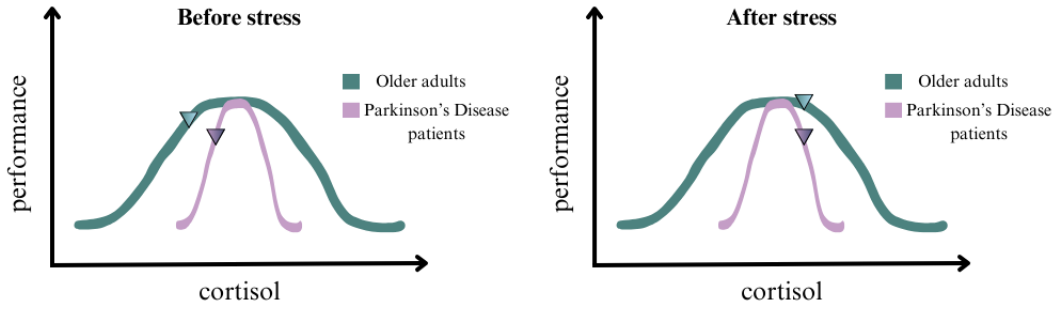

Figure 4-1. Visual depiction of potential differences in inverted u-shaped curve between OA and PD.

This assumption is of course speculative at best, and there is a possibility that PDs instead have no inverted u-shaped curve at all, but if we were to continue this train of thought, the immediate next question is why would there be a narrowing in the curve? As discussed in chapter 3, chronically elevated cortisol levels, as seen in PD, can lead to the downregulation of glucocorticoid and mineralocorticoid receptors which are expressed in the prefrontal cortex and hippocampus, essential areas for executive functioning (de Kloet et al., 2005; Hinkelmann et al., 2009; Opinion et al., 2023; Rich & Romero, 2005; Shrimpton & Randall, 1994; Soares et al., 2019). So perhaps, although the cortisol increase is present following acute stress, the chronic cortisol levels have caused a downregulation in the brain, hence reducing the beneficial acute stress effects of cognition that we observe in our OA sample.

Another possible explanation stems from the relationship between acute stress, cortisol and dopamine. Acute stress, and specifically cortisol, has been shown to increase dopaminergic activity in both animal and human models, with strongest effects on the striatum and prefrontal cortex in humans (Finlay et al., 1995; Nagano-Saito et al., 2013; Oswald et al., 2005; Payer et al., 2017; Stelly et al., 2020; Vaessen et al., 2015). Chronic stress also seems to influence dopamine levels,

although the literature here is less clear indicating either little to no effect or decreases in dopamine levels (Bloomfield et al., 2019; Finlay et al., 1995; Roth et al., 1982). Furthermore, dopamine, similar to cortisol, is thought to have an inverted u-shaped effect on cognition (Cools & D'Esposito, 2011), so perhaps the improvement in cognition following acute stress in OAs is actually due to the downstream increase in dopamine, and not from the increase in cortisol itself. In PDs, there is often a dysfunction in dopamine production, so if the cortisol increase cannot trigger increase dopaminergic activity, then perhaps this is the reason for the absence of the beneficial stress effects on cognition. Alternatively, since all PD participants were On medication, perhaps there is a ceiling effect on the dopaminergic activity and that the increased cortisol levels have no effect on dopaminergic activity since a maximum level has already been reached. Much more detailed work is clearly needed on the effect of acute and chronic stress on the brain in PD that involves measurements of stress biomarkers and of the wide range of cognitive processes that can be influenced by stress.

4.4 Future directions

First, it is important to recognize that unlike in chapter 2, when looking at PDs response to acute stress, we did not examine for the possible modulating effect of sex, which, as observed in chapter 2 and prior literature, can modulate the effects of acute stress on mood, physiology and cognition (Hidalgo et al., 2019; Kudielka & Kirschbaum, 2005; Liu et al., 2017; Wood et al., 2001). Studies often attribute sex differences to female reproductive hormones with some studies having shown that female sex hormones can be protective towards the detrimental effects of stress on physiology and cognition (Kajantie & Phillips, 2006; Wei et al., 2014). Considering the older age of our sample in both chapter 2 and 3 it is important to consider the role of these sex hormones. With menopause, female sex hormones decrease and, with them, so do their protective effects. However, these protective effects on both physiology and cognition could be restored with hormone replacement therapy which is not uncommon for perimenopausal and menopausal women (Herrera et al., 2017; Kudielka et al., 1999; Lindheim et al., 1992). Mechanistically, estrogen is thought to suppress mineralocorticoid receptor regulation (Barrett Mueller et al., 2014; Ter Horst et al., 2013) which, as observed in Chapter 3, could potentially be downregulated in PD patients due to chronically elevated cortisol levels. Therefore, there could be merit in exploring the interaction of

sex on acute stress responses, especially in patient populations who are suspected of experiencing chronic stress.

Chapter 3 introduced blood pressure as a physiological measure of acute stress, which falls under the fast-acting sympathetic-adreno-medullar (SAM) system, however this is only one of many physiological markers pertaining to this system. Another key element of the SAM system is salivary alpha amylase (sAA), which has shown elevation following acute stress in both younger and older adults and is well-associated with elevations in cortisol (Almela, Hidalgo, Villada, van der Meij, et al., 2011; Pulopulos et al., 2015; Schoofs et al., 2008, 2013). Some studies also examined the effect of aging on sAA response to acute stress but again, have found conflicting results (Almela, Hidalgo, Villada, van der Meij, et al., 2011; Strahler, Mueller, et al., 2010). Outside of stress literature, sAA has also been featured in PD research as a potential biomarker of disease severity however no clear pattern has been established with some studies suggesting lowered and others elevated levels of sAA in PD (Ali & Nater, 2020; Kawabe et al., 2012; Masters et al., 2015; Mukaiuama et al., 2021; Salaramoli et al., 2023). Considering the relevance of sAA in both acute stress literature and PD literature, a logical next step would be to investigate the effects of acute stress on sAA in PD with hopes of uncovering a potential interaction PD and sAA response. Some literature has also proposed a role of chronic stress in sAA levels suggesting overall elevations (Nater et al., 2007; Strahler, Berndt, et al., 2010; Vineetha et al., 2014) and one study has suggested the use of a sAA to cortisol ratio as a measure of chronic stress (Ali & Pruessner, 2012). Therefore, not only would the addition of sAA into future acute stress studies on PD be of benefit, it could also provide insight into the interaction between acute and chronic stress.

4.5 Conclusions and significance

Together, these two studies offer a comprehensive exploration into the intricate relationship between acute stress and mood, physiology and cognition, particularly within the realms of older adults and PD patients. The first study, encompassing a diverse middle and older-aged population, challenges conventional wisdom by revealing stress-induced improvements rather than impairments in working memory and executive functions, demonstrating a sex-dependent variation in the stress-response paradigm. The second study is, to our knowledge, the first to

examine the affective, physiological, and cognitive responses to acute stress in PD patients. The results revealed a blunted affective response, challenging assumptions about emotional processing deficits in PD, and suggested that stress levels may be chronically elevated, even in neutral conditions. Shared physiological responses between PD patients and older adults suggest similarities in physiological stress reactivity across these populations, while the absence of cognitive benefits, particularly in working memory, poses crucial questions about potential downregulation mechanisms in the brain. These findings have significant implications for understanding the non-motor symptoms of PD and illustrate that the impact of stress is not uniform across OAs and PDs, emphasizing the need for tailored approaches to understanding and managing stress-related issues, especially in neurodegenerative diseases like PD. Together, these studies enrich our understanding of the diverse responses to acute stress, paving the way for future investigations that delve deeper into the underlying mechanisms and lay the groundwork for potential interventions.

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