Linking Motivation to Effort and Reward Processes in Older Adults in Health and Chronic Illness

Gloria Rebeca Castaneda Pizana

Integrated Program in Neuroscience

McGill University, Montreal, Quebec, Canada.

A thesis submitted to McGill in partial fulfillment of the requirements of the degree of the degree of Doctor of Philosophy.

Table of Contents

Abstract

We make decisions on a daily basis as to whether we engage in effortful goal-directed behaviors. We do so by evaluating the potential costs and benefits associated with such decisions. The willingness to engage in effortful behaviors varies across individuals and is affected by aging, mental health conditions, and other chronic illnesses. Despite its importance to function and quality of life, motivation remains poorly understood. What makes one person more motivated than another? How do health conditions sap motivation? Decision neuroscience provides frameworks for dissecting motivation into its component parts, but these are just beginning to be applied to understand the low motivation seen in chronic health conditions. This doctoral work presents three studies that investigate the relationship between different putative component processes of motivation and self-report indicators of real-world motivation. Chapter 1 and Chapter 2 provide a general introduction on the methods used to assess motivation, describe some of the gaps between the existing clinical and cognitive neuroscience literatures, and provide background information on the current state of knowledge for motivational disorders in older adults. Chapters 3 and 4 focus on effort-cost decision-making (ECDM) measured with laboratory tasks that assess the willingness to expend effort for monetary rewards. Chapter 3 reports on a study in 80 people with chronic HIV infection. We tested the relationships between the subjective cost of physical and cognitive effort measured with an ECDM task and various indicators of brain health. A relationship was found between ECDM performance and self-reported hours spent on meaningful activity, used as an indicator of motivated behavior. However, ECDM performance was not related to self-reported motivation assessed with items from the Starkstein Apathy Scale, nor to other brain

health measures. Chapter 4 took a critical look at common ECDM tasks, comparing two tasks that require physical effort. A sample of 73 community-dwelling older adults completed a handgrip task similar to the one used in Chapter 3 and a widely-used button press ECDM task. Again, we asked if performance on these tasks was related to various indicators of brain health. We also explored the construct of intrinsic motivation, piloting a new task intended to assess willingness to exert effort to satisfy curiosity. The results showed that these two ECDM tasks cannot be used interchangeably. Indeed, performance was not correlated in this sample. Replicating the results of Chapter 3, neither task related to self-reported motivation. In contrast, there was some evidence for a link between performance on the intrinsic motivation task and self-reported motivation. Chapter 5 narrowed the focus from effort-reward trade-offs to individual variation in the neural response to reward, studied in a new sample of 75 older people with chronic HIV. Electroencephalogram (EEG) was used to measure two reward-related potentials (Reward-Positivity; RewP and feedback-P300; FB-P3) evoked by gain or loss feedback. This chapter provides evidence that EEG activity in response to reward is related to real world motivated behavior. The amplitude of the FB-P3 was associated with self-reported hours spent on meaningful activity. This association was not present for the RewP and was not explained by age or past immunosuppression status. This thesis concludes with Chapter 6, a final section that bridges the findings from all studies, provides a general discussion of the lessons learned in this research and the implications of these findings for assessing and understanding variation in motivation. In summary, this thesis provides evidence that the subjective cost of effort assessed with ECDM tasks and an EEG signal evoked by feedback may be useful tools for understanding real-world motivation. This work is a step towards a clearer

analytic framework and new tools for studying the brain basis of motivated behavior in older adults, in health and chronic illness.

Résumé

Nous devons régulièrement décider s'il en vaut la peine d'accomplir une activité demandant un certain effort afin atteindre divers objectifs. Ceci requiert une évaluation des bénéfices ainsi que des coûts potentiels associés à une décision. La propension à accomplir des tâches demandant un effort varie entre les individus et est affectée par le vieillissement, les troubles de santé mentale et autres maladies chroniques. Malgré l'impact majeur du concept de motivation sur la qualité de vie, ses bases neurologiques demeurent incomprises. Qu'est-ce qui rend une personne plus motivée qu'une autre? Comment les conditions de santés sapent-elles la motivation? Les neurosciences fournissent un cadre pour étudier la motivation en la disséquant en composantes quantifiables. Cette approche commence tout juste à être déployée dans le but de comprendre la diminution de motivation qui accompagne une variété de problèmes de santé chroniques et qui pourrait laisser présager une future dégradation de l'état de santé chez les personnes vieillissantes. Cette thèse de doctorat présente trois études qui examinent les relations entre les différentes composantes présumées de la motivation mesurée en laboratoire, et leurs liens avec des indicateurs autodéclarés du niveau motivation dans la vie quotidienne. Le Chapitre 1 et le Chapitre 2 contiennent une introduction générale à propos des méthodes utilisées pour évaluer la motivation et décrivent certaines divergences entre les connaissances acquises en clinique et en recherche en neuroscience cognitive. Ces Chapitres présentent aussi un aperçu des connaissances actuelles sur les troubles de la motivation, chez les personnes en santé et celles vivant avec des maladies chroniques. Les Chapitres 3 et 4 portent sur l'étude de la prise décision coûteuse en effort (PDCE), mesurée avec des tâches en laboratoire qui évaluent la propension à exécuter un effort pour obtenir une

récompense monétaire. Le Chapitre 3 rapporte une étude chez 80 participants vivant avec une infection chronique au virus de l'immunodéficience humaine (VIH). Le coût subjectif de l'effort cognitif et physique fut évalué avec une tâche de PDCE, mise en relation avec divers indicateurs de santé. Les résultats montrent que la performance à cette tâche était associée à un indicateur autodéclaré de motivation de la vie quotidienne : le nombre d'heures d'activité utile ou significative par semaine. Cependant, cette tâche n'était pas associée avec le niveau de motivation autodéclaré évalué avec l'Inventaire d'Apathie de Starkstein (IAS), ou avec d'autres symptômes de santé mentale. Le Chapitre 4 porte regard critique aux tâches expérimentales de PDCE en comparant directement deux tâches qui requièrent un effort physique. 73 personnes âgées en bonne santé ont complété une tâche qui implique une pression de la main similaire au Chapitre 3, et une autre tâche demandant d'appuyer sur une touche répétitivement. Les résultats montrent que ces deux tâches pourtant fréquemment utilisées pour étudier le même concept de motivation de sont pas interchangeables, puisqu'aucune corrélation n'a été trouvée. Réplicant aussi les résultats du Chapitre 3, la performance à aucune des deux tâches n'était corrélée avec le niveau de motivation autodéclaré mesuré avec l'IAS. Cette étude explore également le concept de motivation intrinsèque en présentant une nouvelle tâche visant à évaluer la propension d'une personne à exécuter un effort pour satisfaire sa curiosité. Les résultats suggèrent qu'il y a une corrélation entre cette mesure de motivation intrinsèque et le niveau de motivation auto-déclaré. Le Chapitre 5 se concentre sur les différences inter-individuelles dans la réponse en réaction à la récompense, étudiés chez 75 participants vivant avec le VIH. L'électroencéphalographie (EEG) fut utilisée pour mesurer deux types de potentiels évoqués associés à la récompense (positivité de récompense; RewP, et FB-

P3). Les résultats suggèrent que l'activité EEG est associée à la motivation. L'amplitude du FB-P3 était corrélé avec le nombre d'heures par semaine passées à faire des activités utiles ou significatives. Cette association n'était pas présente dans le signal EEG RewP, et n'était pas expliquée par l'âge ou l'état passé d'immunosuppression des participants. Cette thèse termine avec le Chapitre 6, une section qui lie les résultats des trois études, et une discussion générale des leçons apprises lors de ces travaux et des contributions de ces résultats à l'évaluation et la compréhension des variations de motivation. Ensemble, ces travaux soutiennent que le coût subjectif de l'effort tel que mesuré avec les tâches de PDCE ainsi que les signaux EEG en réponse à la rétroaction pourraient être des outils utiles pour comprendre la motivation de la vie quotidienne, chez les gens vivant avec le VIH. Ceci est un important pas vers l'établissement d'un carde analytique rigoureux et d'outils expérimentaux précis pour étudier les bases neuronales de la motivation, chez les gens en santé ou vivant avec des maladies chroniques.

Acknowledgments

Firstly, I would like to express my gratitude and admiration to my supervisor, Dr. Lesley K. Fellows for her support, feedback, and lessons throughout my Ph.D., and especially for directing this research project with a great deal of commitment and expertise. I would also like to thank all members of my committee Dr. Nancy Mayo and Dr. Lisa Koski, for all of the additional insight and expertise they brought to these projects. Thank you for all of the long conceptual conversations about motivation and your support, especially during the months where our meetings could not be in person. I would like to acknowledge Dr. Yvonne Yau for her help during the computational analysis of studies one and two of this dissertation, and Dr. Ana-Lucia Fernandez Cruz for all of her contributions in the HIV projects, feedback, insightful conversations, and friendship.

I would also like to thank present and past lab members: Gabriel Pelletier, Matt Pilgrim, Ana S. Hincapie, Maral Yeganeh Doos, and Michael Yeung for their peer support, and stimulating conversations we had over these past years. These acknowledgments are extended to the entire unit of cognitive neuroscience and other members of The Neuro in particular my friends and colleagues Carolina Makowski, Christine Dery, and Stanley Hum for their feedback, analytical skills, and patience when answering all of my questions, and for making it fun to work at The Neuro!

I am grateful to have had the opportunity to be part of the Neuro and Positive Brain Health Now project and have met an incredible team of researchers, students, and participants. Dr. Marie-Josee Brouillette, Susan Scott, and Melissa Vu, thank you for all the support given to these projects including but not limited to recruitment, project management, and data analysis.

I would also like to acknowledge all the funding sources: CONACYT, The Velux Foundation, the Canadian Institutes of Health Research and the Canadian Institutes of Health Research HIV Clinical Trials Network, and the Healthy Brains for Healthy Lives who made these projects possible.

Thanks to my friends and family especially Caitlin, Mariana, and Eric, who accompanied me in this journey and were there through all of the ups and downs, always patient and supportive. I feel lucky to have my mom Gabriela, my sister and grandmother, who are an example of determination and empowerment in my life. Thank you for your support in pursuing this doctoral degree. I am forever grateful for all of your unconditional love and support.

Contributions to Original Knowledge

In accordance with the guidelines of McGill University Graduate and Postdoctoral Studies for a manuscript-based thesis, the contributions of each author are described here. This thesis integrates original research in three manuscripts:

Chapter 3

Castaneda G., Fernandez-Cruz A.L., Sefranek M., Yau Y., Brouillette M.J., Mayo N.E. & Fellows L.K. Does Effort-Cost Decision-Making Relate to Real-World Motivation in People Living with HIV? *Submitted to Journal of Clinical and Experimental Neuropsychology.*

Chapter 4

Castaneda G., Mayo N.E., Koski L. & Fellows L.K. Comparison of Effort-Cost Decision-Making Tasks and their Relation to Self-Reported Motivation in Community-Dwelling Older People. *To be submitted for publication*.

Chapter 5

Castaneda G., Fernandez-Cruz A.L., Brouillette M.J., Mayo N.E. & Fellows L.K. Reward-Related Evoked Potentials as Markers of Low Motivation in Older People Living with HIV. *To be submitted for publication*.

For all three studies, Dr. Lesley K. Fellows contributed to the initial conception and provided advice during data analyses and critical revision and final approval of the manuscripts and Dr. Nancy E. Mayo contributed to the analysis and interpretation of the data for all three studies.

For Chapter 3 (study 1), Gloria Castaneda collected and performed analysis of the data and wrote the manuscript. Dr. Ana Lucia Fernandez Cruz and Marcus Sefranek helped in the initial study design, collection of pilot data, and programmed of the experiment. Dr. Yvonne Yau contributed to the analysis of the data. For Chapter 4 (study 2), Gloria Castaneda designed and programmed the experiments, collected, and performed analyses of the data contributed to the literature review and wrote the manuscript. For Chapter 5 (study 3), Gloria Castaneda reviewed the literature and planned the analysis, preprocessed, extracted, and analyzed the data, and wrote the manuscript. Dr. Ana Lucia Fernandez Cruz programmed the experiment and collected the behavioral and electrophysiological data.

The participants involved in the studies reported in Chapter 3 and Chapter 5 were drawn from the Positive Brain Health Now (BHN) cohort, a Canadian longitudinal study of brain health in persons with HIV. This CIHR-supported study involved 28 co-investigators. Marie-Josée Brouillette and Lesley K. Fellows are Principal Investigators, and Nancy E. Mayo leads the data management team. Recruitment of the cohort and collection and management of the demographic, clinical, and cognitive data were done by members of the BHN team.

List of Figures

List of Tables

Abbreviations

ACC= Anterior Cingulate Cortex

AD= Alzheimer Disease

AES= Apathy Evaluation Scale

AI= Anterior Insula

AIDS= acquired immunodeficiency syndrome

ANI= asymptomatic neurocognitive impairment

B-CAM= Brief Cognitive Ability Measure

B0= Bias model parameter; selection of a "no" response.

BBB= Brain Blood Barrier

Be= Effort model parameter.

BHN= Brain Health Now Cohort

Br= Reward model parameter.

C3Q= Communicating Cognitive Concerns

cART= combination of antiretroviral therapy

CI= Confidence Interval

CNS= Central Nervous System

dACC= Dorsal Anterior Cingulate Cortex

DS= Dorsal Striatum

ECDM= Effort-Cost Decision Making

EEfRT= Effort Expenditures for Rewards Task

EEG= Electrophysiology

ERP= Event-Related Potential

ERT = Effort Reward Trade-Off

fMRI = functional magnetic resonance imaging

FRN= Feedback-Related Negativity

gp120= glycoprotein 120

HAART= highly active antiretroviral therapy

HAD= HIV-associated dementia

HADS= Hospital Anxiety and Depression Scale

HAND= HIV-Associated Neurocognitive Disorders

HIV= Human Immunodeficiency Virus

IMT= Intrinsic motivation task

LARS= Lille Apathy Rating Scale

MCC= Midcingulate Cortex

MDD= Major Depressive Disorders

MFG= Middle Frontal Gyrus

MND= HIV-associated mild neurocognitive disorder

MOCA= Montreal Cognitive Assessment

mPFC= Medial Prefrontal Cortex

MRI= magnetic resonance imaging

nACC= Nucleus Accumbens

OFC= Orbitofrontal Cortex

PCC= Posterior Cingulate Cortex

PD= Parkinson's Disease

RewP= Reward Positivity

SAS-R= Starkstein Apathy Scale-Rasch

SAS= Starkstein Apathy Scale

sgACC= Subgenual Anterior Cingulate Cortex

SMA= Supplementary Motor Area

STG= Superior Temporal Gyrus

STN= Subthalamic Nucleus

vmPFC= Ventral Medial Prefrontal Cortex

VS= Ventral Striatum

Chapter 1

Introduction

General Introduction and Thesis Overview

Low motivation is common in chronically ill older people and is recognized as a threat to successful aging even in the otherwise healthy elderly (Bock, Bahorik, Brenowitz, & Yaffe, 2020; Semprini, Lubrano, Misaggi, & Martorana, 2012). While motivation is affected in many neurological and psychiatric disorders and has been linked to worse health outcomes, the brain basis of this behavior remains poorly understood.

Motivation is considered a core feature of the apathy syndrome (together with emotional blunting and lack of concern about one's health condition) (Mann, 1990; Marin, Biedrzycki, & Firinciogullari, 1991; Marin & Wilkosz, 2005a) and is most often measured with self-reported apathy scales. The psychometric properties of some scales may be suboptimal, at least in people with neurological disorders (Hum, Fellows, Lourenco, & Mayo, 2021; Lourenço, 2014). The relationships between low motivation and other aspects of apathy, as well as other potentially relevant symptoms that are also common in such patients, including depression, cognitive impairment, and fatigue, remain unclear. Finally, questionnaire measures of apathy assess behavior at a rather coarse level of resolution that is challenging to map to specific brain regions or circuits. To bridge the gap between the clinic and neuroscientific research, it will be necessary to focus on motivation, and then to drill down further, to identify components of

motivation that might be more easily linked to the brain, if a neurobiologically-informed model of motivation is to emerge.

This dissertation examines the relationship between individual differences in motivation in older people in health and chronic illness and specific behavioral tasks and EEG measures of candidate component processes, i.e. the subjective cost of effort assessed with effort-cost decision-making (ECDM) tasks, and the neural response to gain or loss feedback. The three projects presented in this thesis contribute to bridging the gap between the clinic and fundamental neuroscience by providing a better understanding of the construct of motivation, improvements in assessing component processes of motivation, and preliminary insights into the underlying brain circuits.

In the next chapter, I will first present a conceptual overview of motivation, from the first definitions and studies in psychology to the clinical diagnostic criteria of apathy. I will then review the neuroscience literature, focusing on ECDM. The subsequent two chapters focus on ECDM task performance and the relationship between such tasks and real-world motivation. The Chapter 5 describes a study focusing even more specifically on EEG responses to gain and loss feedback in a simple guessing task. Of these three original research studies, two are in older people living with human immunodeficiency virus (HIV), a clinical sample where low motivation is prevalent. The study assessing the validity of ECDM tasks was conducted in community-dwelling older adults. Overall implications of the findings and lessons learned in these studies will be discussed in the concluding chapter.

Chapter 2

Literature Review

Clinical Conceptual Framework of Apathy

Apathy, a syndrome characterized by loss of or diminished motivation, became a focus of study after World War I, when it was recognized as a clinical disorder in soldiers who developed indifference to normal interactions in the context of "shell shock" (Greenson, 1949). Similar changes in behavior were subsequently recognized in patients with schizophrenia, multiple sclerosis, Parkinson's disease (PD), and dementia, as well as after stroke and substance withdrawal (Brower, Maddahian, Blow, & Beresford, 1988; M. L. Levy et al., 1998; Roy, Riggs, Martin, Ringel, & Gutmann, 1988; Schaefer & Martin, 1966). Different diagnostic criteria were proposed to characterize these clinical-behavioral observations, informing the development of various self-report and interview assessments that are currently used in both the clinic and research. One widely used diagnostic framework was proposed by Marin (Mann, 1990), forming the basis of the Apathy Evaluation Scale (AES) (Marin et al., 1991).

Marin proposed that apathy is a syndrome characterized by lack of or reduced motivation, indicated by: a) Diminished goal-directed overt behavior, b) Diminished goal-directed cognition (i.e. lack of interest in learning new things, lack of concern about one's health), and c) Diminished emotional concomitants of goal-directed behavior (i.e. unchanging affect, lack of emotional responsivity, flat affect, absence of excitement or emotional intensity) (Mann, 1990). Subsequently, other authors argued that apathy was only an emotional state, defining it as "a lack of emotional sensitivity" (Sims, 2003). Others suggested that apathy was

better assessed objectively, in terms of an observable and quantified reduction in self-generated voluntary and purposeful behavior, and distinguished cognitive, emotional, and behavioral subtypes (R. Levy & Dubois, 2006). These authors proposed that apathy could arise from dysfunction in any of the different stages necessary to achieve such goal-directed behavior, rather than as a subjectively reported state. In 1992 and again in 2008, Starkstein and Leentjens modified the AES as the Starkstein Apathy Scale (SAS) (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992). They proposed that apathy was principally a disorder of motivation, and limited the emotional domain of apathy to a diminished concomitant of goal-directed behavior evidenced by an unchanging or flat affect or by a lack of emotional responsivity to positive or negative events (S. . E. Starkstein & Leentjens, 2008). This work has been applied to diagnose apathy and differentiate it from other disorders and has since become the most widely used self-report assessment for measuring apathy.

Since then, two other diagnostic criteria have been proposed for apathy in brain disorders (Robert et al., 2018) and neurocognitive disorders (Miller et al., 2021). To facilitate objective quantification, both the diagnostic criteria for brain disorders and neurocognitive disorders replaced the term ‘motivation’ with ‘goal-directed behavior’. Given the complexity of apathy, cognitive neuroscientists focus on motivation as expressed in goal-directed behavior, and further break down motivation into more basic component processes that can be studied using focused behavioral tasks. The work presented here will use the definition of apathy as a syndrome characterized at its core as a loss of motivation, with a focus on the behavioral domain.

Existing Self-Reported Measures of Apathy and their Limitations.

Apathy has been assessed qualitatively through clinical assessment or by using self-reported questionnaires. Among the most popular assessments are the Lille Apathy Rating Scale (LARS) (Sockeel et al., 2006), a clinician assessment tool initially designed for PD, and the SAS (S. . Starkstein et al., 1992), which is the apathy scale based on the AES discussed above (Marin et al., 1991). While some concerns have been raised regarding the degree of capability some patients might have in effectively reporting on apathy symptoms in self-report measures (Cysique & Brew, 2019; Robert et al., 2018) (due to anosognosia, for example), self-report is more feasible in research. However, there are several limitations of using these assessments either clinician assessments or self-report, in research. The LARS has good psychometric properties, but has a complicated scoring system and requires a clinician (Mccusker, 2015), and the widely used 14-item SAS has psychometric limitations at the item level. For instance, research from our group found that, some items are redundant and others are confusing (Hum et al., 2021; Lourenço, 2014). Other options, like the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) and the Positive and Negative Symptom Scale (Kay, Fiszbein, & Opler, 1987) are not specific to apathy, encompassing other constructs such as anhedonia, asociality, blunted affect and alogia (i.e. poor speech quality), in addition to amotivation (Blanchard & Cohen, 2006; Millana, Fone, Steckler, & Horan, 2014) (Mccusker, 2015). These commonly co-exist in schizophrenia, a condition where apathy has been a particular focus of study. Table 2.1 presents a summary of some of the most common measures of apathy used in the clinic.

Table 2.1

Characteristics of widely-used clinical apathy measures

Apathy Measure	Number of items	Type of scale	Group
Apathy Evaluation Scale (AES; Marin 1990)	18	Self-report or Informant or clinician interview.	Healthy Individuals
Apathy Scale (SAS; Starkstein et al, 1992)	14	Self-report	PD
Apathy subscale of the Neuropsychiatric Inventory (NPI; Cummings et al. 1994)	7	Clinician administered	Dementia, AD
Dementia Apathy Interview and Rating (DAIR; Strauss and Sperry 2002)	16	Clinician administered	AD
Positive and Negative Symptom Scale (PANSS; Kay et al. 1987)	7-item subscale (30 total)	Clinician administered	Schizophrenia
Frontal System Behavior Scale (FrSBe; Grace and Malloy 2001)	14-item subscale (46 total)	3 forms available: Self, family, and staff.	Fronto-temporal deficits
Lille apathy rating scale (LARS; Sockeel et al. 2006)	33	Clinician administered	PD

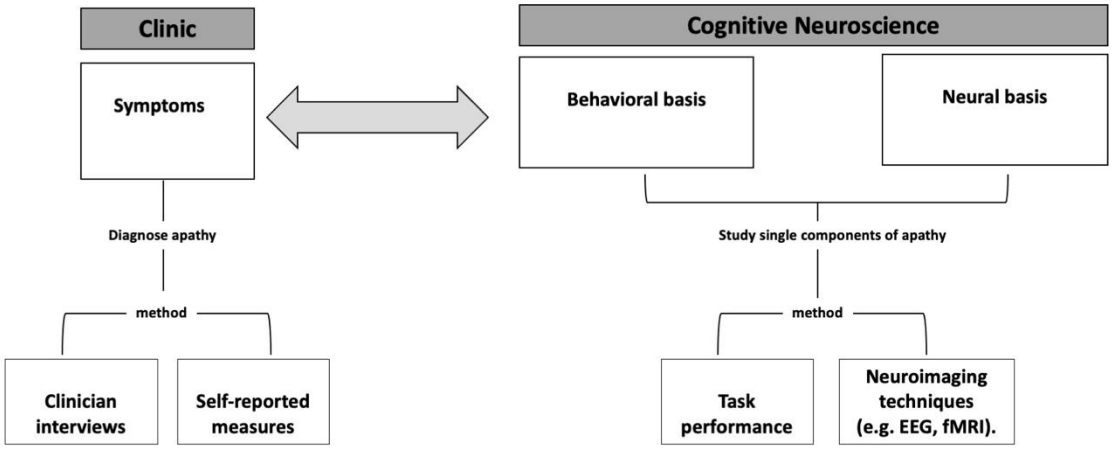
Note: Parkinson's disease, PD; Alzheimer's disease, AD.

Motivation: A Complex Construct.

The lack of a gold-standard measure of apathy is in part because apathy is a complex behavioral syndrome, making it challenging to assess and study. Figure 2.1 shows a diagram of the different methods used in the clinic and in cognitive neuroscience to study apathy and motivated behavior.

Figure 2.1

Schematic framework showing clinical and cognitive neuroscientific approaches to apathy.



Note: In the clinic, symptoms are the primary outcome and are measured by clinician interviews and self-report measures. In cognitive neuroscience, behavioral and neural outcomes are used to study specific aspects of apathy, with goal-directed behavior further divided into simpler components that can be operationalized using focused tasks and potentially related to definable brain circuits through functional or structural neuroimaging methods.

Motivation: From Psychology to Neuroscience

Neuroscience research relevant to clinical apathy has focused more narrowly on motivation. Motivation is itself a multifaceted construct that is involved in the initiation, direction and continuation of goal-directed behavior. The term originates from Latin and means "to move"; however, there is no consensus for a clear definition across disciplines (Frey &

Jegen, 2001; Nevid, 2012; Strombach, Strang, Park, & Kenning, 2016). More recent work defines goal-directed behavior as behavior aimed towards a goal or completion of a task; when disrupted, this can be a feature of the clinical syndrome of apathy (Robert et al., 2018). The first studies of motivation in psychology focused on motives based on biological instincts. It was later proposed that motives could be inherent and central to survival or learned through experience. Three categories of motives were then suggested which all lead to motivated behavior: biological motives (i.e. including instincts, drives, etc.), psychological motives (i.e. intrinsic and extrinsic, self-determination, self-actualization and social), and economic motives (i.e. monetary incentives, performance, and preferences) (Strombach et al., 2016).

Motives may also be categorized as extrinsic or intrinsic. Extrinsic motives are external factors (i.e. money or food) whereas intrinsic motives are inherent to the behavior itself (Ryan & Deci, 1985). For example, you might read a book because you want to learn (extrinsic motive) or because you enjoy reading (intrinsic motive). In these two scenarios, each of the two motives (i.e. learning and inherent pleasure of reading) could lead to engaging or not in the behavior.

The field of cognitive neuroscience has behavioral economic principles as a starting point for studying motivation. A widely-used framework focuses on cost-benefit analysis of behavioral options (Simpson & Balsam, 2015). That is, the amount of expected effort (i.e. the cost) an organism is willing to produce for an expected benefit. The value of a stimulus is multifactorial and subjective as it depends on several internal and external factors (e.g., previous experiences, hedonic properties, etc.) (Studer & Knecht, 2016). In line with psychological theories of motivation, the benefits could be intrinsic or extrinsic and the costs could be of various types (e.g., cognitive effort, physical effort, time, etc.) (Fellows, 2004;

Glimcher & Rustichini, 2004; Simpson & Balsam, 2015). For this dissertation, I will consider physical and cognitive effort-costs and both extrinsic and intrinsic rewards.

Cognitive Neuroscience Framework of Motivation

The cognitive neuroscience work on motivation has applied frameworks of goal-directed behavior that include considerations of costs and benefits of behavior, as well as the processes that preceded and followed such cost-benefit analysis. Primarily, I will follow the framework proposed by Husain & Roiser (2018) as it is centered on effort, but some elements from other decision-making frameworks are integrated as well (Barch, Pagliaccio, Luking, Moran, & Culbreth, 2019; Fellows, 2004; Husain & Roiser, 2018)

The cognitive neuroscience framework of motivation gives a more detailed view of what is at play in goal-directed behavior. In the next sections, I will summarize some of the findings of each of these component processes, as well as how they have been assessed in the literature.

1. ***Option generation*** is the component of goal-directed behavior that initiates every decision-making process. This stage could be self-generated or initiated by an external factor (i.e. another individual or the environment). Impairment in the ability to come up with options is one characteristic of apathy and is included as an item in some of the self-reported assessments used in the clinic (Fellows, 2004; Husain & Roiser, 2018).

2. ***Effort-Cost Decision Making (ECDM)***. This next stage is part of the *evaluation* stage proposed in other decision-making frameworks (Fellows, 2004), and can interact with other factors like intrinsic properties of the stimulus, risk or probability of obtaining the reward, temporal discounting, reward satiation, or effort. The effort component evaluates the cognitive or physical effort required to obtain a reward. The subjective value of the reward and the

subjective cost of effort are valued individually and might be useful information in identifying apathetic behavior. Theories of motivation suggest that someone with low motivation will either value effort as more costly or reward as less beneficial and consequently will not initiate or sustain goal-directed behaviors (Barch et al., 2019; Husain & Roiser, 2018). A review of studies on ECDM in healthy and clinical populations is presented in the next chapters.

Studies on Motivation and Effort-Cost Decision Making.

As described in the previous section, one central element of motivation is the willingness to work to achieve a goal. This was initially operationalized in animal research (reviewed in (T. T.-J. T.-J. Chong et al., 2017)) and subsequently, conceptually similar tasks have been developed for humans. Amongst the most widely used is the Effort Expenditures for Reward Task (EEfRT) by Treadway et al. (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009). A diagram of the various types of ECDM paradigms used in both humans and animals is represented in Figure 2.2. This task has been mainly used to study motivation in schizophrenia (Barch, Treadway, & Schoen, 2014; Fervaha et al., 2015, 2013; McCarthy, Treadway, Bennett, & Blanchard, 2016; Treadway, Peterman, Zald, & Park, 2015) and in response to dopamine manipulations in healthy people (Treadway, Buckholtz, et al., 2012; Wardle, Treadway, Mayo, Zald, & de Wit, 2011). Other variations of effort-reward tasks use squeezing a handgrip dynamometer as the physical effort requirement (Bonnelle, Veromann, et al., 2015; Draper et al., 2018; Le Heron, Plant, et al., 2018) and more recently, similar task designs have measured willingness to produce cognitive effort (Dobryakova, Jessup, & Tricomi, 2017; Hughes, Yates, Morton, & Smillie, 2015; Sandra & Otto, 2018) in return for monetary rewards. These ECDM paradigms require weighing the subjective value of effort and the subjective value of the reward to make a choice. The

expectation is that if an individual is less motivated, the subjective cost of effort will be higher, or the subjective value of the reward will be lower, i.e. it will require a higher monetary amount for a given level of effort to be chosen (T. T.-J. T. J. Chong, Bonnelle, & Husain, 2016). Several studies have found a reduced willingness to expend effort for rewards in people with schizophrenia, PD and major depression disorder (MDD) compared to healthy controls (Barch et al., 2014; T. T.-J. Chong et al., 2015; Cléry-Melin et al., 2011; Fervaha et al., 2013; Gold et al., 2013; Hershenberg et al., 2016; Horan et al., 2015; Huang et al., 2016; Le Bouc et al., 2016; Porat, Hassin-Baer, Cohen, Markus, & Tomer, 2014; Treadway, Bossaller, Shelton, & Zald, 2012; Treadway et al., 2015). However, whether the observed reduction in the willingness to exert effort is related to apathy severity or other symptoms has been far less studied, with mixed results in the available literature (Docx et al., 2015; Fervaha et al., 2013; Gold et al., 2013; Hartmann et al., 2015; Huang et al., 2016; Treadway et al., 2015). Determining this relationship is relevant to bridging the gap between fundamental cognitive neuroscience and the clinic. It is also important to know whether ECDM tasks are specifically related to motivational symptoms, or are also related to other mood, behavioral or cognitive symptoms.

Effort Expenditure in Healthy Older Adults.

While there is an extensive literature on some cost-benefit decision-making processes (e.g. delay and risk) in older adults, research on effort valuation is limited, particularly in older people who often suffer from loss of motivation. In this section, I will describe the implications of aging on effort-cost decision making with a focus on cognitive effort, as there are few studies on aging and physical effort.

Throughout the lifespan, effort expenditure is consistently viewed as a costly endeavor, and if given a choice, individuals prefer to avoid effortful actions. However, there is some evidence that the way in which these valuations are made differs with age. In general, it is suggested that compared to younger people, older people perform worse in tasks that require the integration of new information, whereas their performance remains intact or is even enhanced when it relies on previously established representations (Samanez-Larkin & Knutson, 2015). There is also evidence that aging increases the subjective perception of cognitive effort expenditure, independent of tasks demands, and that this consequently influences the willingness to engage in cognitive tasks that older people perceive as demanding (Ennis, Hess, & Smith, 2013; T M Hess & Ennis, 2012, 2014; Thomas M. Hess, Smith, & Sharifian, 2016). Older adults also show higher levels of fatigue in cognitive effort tasks compared to younger adults (Westbrook et al., 2013), which may also impact how older adults valuate effort costs.

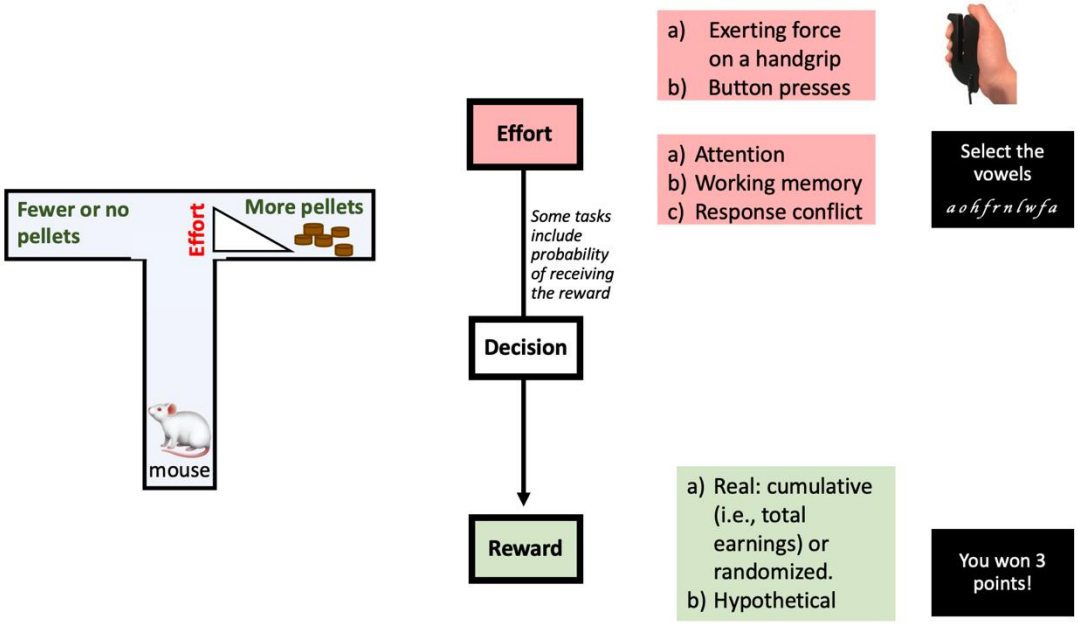
None of the above studies addressed whether other constructs, apart from fatigue had an impact on the valuations of cognitive effort. Other studies on different costs have demonstrated associations between greater delay discounting and greater risk aversion in individuals with significant cognitive decline (Han et al., 2016; James, et al. 2015). Other studies also suggest that older individuals may present an increased sensitivity to the costs associated with risk-taking (Samanez-Larkin et al., 2015).

The findings of studies applying ECDM tasks in clinical and healthy populations will be systematically reviewed in Chapter 4. As mentioned, these paradigms are focused on the tradeoff of effort and reward, which call on cognitive ability generally but also include specific requirements of reward anticipation and assessing the subjective cost of effort. Studies using

ECDM tasks have shown that clinical populations have a higher subjective cost of effort compared to healthy people, but whether this higher subjective cost of effort is related to clinical symptoms like apathy is less clear. In the next section, I will review some of the imaging studies conducted on ECDM to bring together these results.

Figure 2.2

Experimental tasks operationalizing ECDM in animals and humans



Note: To the right of the figure some examples of ECDM in humans are shown for both physical and cognitive effort. To the left of the figure a T-maze paradigm used to measure ECDM in mice is presented.

Neuroimaging Studies of Motivation Using Effort and Reward.

A summary of imaging studies using effort or ECDM paradigms in humans is presented in Table 2.2. This table illustrates the associations between ECDM task outcomes (i.e. effort, reward, or the valuation of effort and reward) at different points in the decision process (i.e. reward anticipation, selecting the choice, reward outcome, etc.). The search terms included effort, decision-making, brain, imaging, and neuroanatomy. The search was conducted in June 2017 with the assistance of a librarian at the Montreal Neurological Institute and Hospital on Ovid

MEDLINE and PsycINFO databases. The areas more widely identified across the literature underlying effort-reward computations are anterior cingulate cortex (ACC), dorsal ACC, and nucleus accumbens (NAcc). Most studies have used either the EEfRT or a variation of a standard effort task. In Table 2.2. the neural areas linked to the interaction of effort and reward processes are marked as effort-reward tradeoff (ERT), and results that linked dopamine with more willingness to exert effort are shown as DA>E.

Table 2.2

Summary of imaging studies of effort and reward in humans

Study	Sample	N	Behavioral contrast	Effort type	Technique	Main findings
Treadway et al.(2012)	Healthy	25	Effort exertion	Physical	PET_1	DA>effort ERT areas: vmPFC, NAcc
MacDonald et al.(2014)	PD	22	Effort exertion	Mental	fMRI	Null findings: DS
Porat et al.(2013)	PD	25	Effort exertion	Physical	NA_2	DA>effort
Bonnelle et al.(2015)	Healthy	37	Decision	Physical	MRI/fMRI	ERT: vmPFC, dACC Effort: NAcc, Putamen
Klein et al.(2016)	Healthy	24	Decision	Physical	fMRI	ERT: dACC
Kurniawan et al.(2010)	Healthy	18	Decision	Physical	fMRI	ERT: NAcc Effort: Putamen
Massar et al.(2015)	Healthy	23	Decision	Mental	fMRI	ERT: ACC
Mulert et al.(2008)	Healthy	10	Decision	Mental	EEG/fMRI	Effort: ACC
Yang et al.(2016)	MDD vs HC	25	Decision	Physical	fMRI	ERT: STG, Caudate
Scholl et al.(2015)	Healthy	21	Decision & Reward outcome	Physical	fMRI	ERT: dACC, AI
Kurniawan et al.(2013)	Healthy	19	Effort anticipation	Physical	fMRI	Effort: ACC Reward: Insula, VS, NAcc Null findings: vmPFC
Zénon et al.(2015)	Healthy	12	Effort perception	Physical	cTBS	Effort: SMA
Burke et al.(2013)	Healthy	23	Option presentation	Physical	fMRI	ERT: MCC Null findings: vmPFC
Vassena et al.(2014)	Healthy	25	Option presentation	Mental	fMRI	ERT: PCC, ACC, Striatum Effort: MFG, AI
Schmidt et al.(2012)	Healthy	20	Reward anticipation	Mental & Physical	fMRI	Reward: VS

Skvortsova et al.(2014)	Healthy	20	Reward anticipation	Physical	fMRI	ERT: dACC, AI Reward: vmPFC
Botvinick et al.(2009)	Healthy	45	Reward cue	Mental	fMRI	ERT: NAcc Effort: ACC Reward: mPFC, OFC Null findings: dACC
Croxson et al.(2009)	Healthy	16	Reward cue	Physical	fMRI	ERT: dACC, VS, NAcc Effort: Putamen Reward: OFC, AI Null findings: vmPFC
Zénon et al.(2016)	PD	12	Reward cue	Physical	DBS	DA>effort ERT:STN
Hernandez et al.(2014)	Healthy	30	Reward outcome	Mental	fMRI	ERT:sgACC

Note: Effort reward trade-off, ERT; supplementary motor area, SMA; middle frontal gyrus, MFG; subthalamic nucleus, STN; superior temporal gyrus, STG; medial prefrontal cortex, mPFC; ventral medial prefrontal cortex, vmPFC; orbitofrontal cortex, OFC; posterior cingulate cortex, PCC; midcingulate cortex, MCC; anterior cingulate cortex, ACC; subgenual anterior cingulate cortex, sgACC; dorsal anterior cingulate cortex, dACC; anterior insula, AI; dorsal striatum, DS; ventral striatum, VS; nucleus accumbens, NAcc. Region of interest; ROI.

[1] DA agonist (d-amphetamine)

[2] ON and OFF DOPA

In line with these findings, a recent meta-analysis of ECDM studies using functional magnetic resonance imaging (fMRI) revealed that areas of the brain linked to reward in ECDM were the ventral striatum (VS), ventromedial prefrontal cortex (vmPFC), and the midbrain. Areas linked to effort were the anterior insula (AI) and anterior cingulate cortex (ACC) (Pessiglione, Vinckier, Bouret, Daunizeau, & Le Bouc, 2018). The same review also proposed that the dorsal ACC could be a region involved in the integration of costs and benefits to compute a net value.

In addition to human ECDM research, such research has also been conducted in animal models. Various paradigms similar to human ECDM tasks exist, where animals are offered food in exchange for effort or are offered a preferred food in exchange for high effort, see figure 2.2 for an example. This research has mainly focused on the role of dopamine in motivation. These studies showed that depletion of dopamine in the nucleus accumbens is associated with avoidance of high effort, due to effort avoidance and not reward or motor impairment (Le Heron, Holroyd, Salamone, Husain, & Heron, 2018; J. D. Salamone, Correa, Farrar, & Mingote, 2007; John D Salamone, Yohn, López-Cruz, San Miguel, & Correa, 2016).

3. ***Anticipatory phase***. After the effort-cost decision-making phase and selection of a choice, anticipation of reward occurs.

4. ***Action preparation***. The anticipatory phase is followed by action preparation, where motor preparation takes place.

5. **Action initiation.** Immediately follows action preparation. This stage includes the initiation of the action and sustainment.

6. **Initial response to reward & interaction with the goal.** The consummatory phase of goal-directed behavior is the *interaction with the goal* or *initial response to reward*,

referring to a hedonic response that can have a positive or negative impact. Reward anticipation and initial response to reward are part of the construct of reward responsiveness (Barch et al., 2019; Husain & Roiser, 2018).

Studies on Motivation and Reward Responsiveness

Very few studies have investigated reward responsiveness in relation to apathy, but some have found evidence for reduced response to reward and symptoms of apathy. For instance, higher apathy symptoms (measured with AES) were linked to decreased activation of the VS using fMRI during *reward anticipation* in participants with schizophrenia (Simon et al., 2010).

Response to reward has been measured using electrophysiology, specifically the amplitude of the Reward Positivity (RewP), an evoked potential that has a more positive peak after positive feedback or gains (Glazer, Kelley, Pornpattananangkul, Mittal, & Nusslock, 2018; Proudfit, 2015). This RewP has been found to be significantly smaller in apathetic patients compared to non-apathetic patients (measured with AES) with PD during a gambling task (Martinez-Horta et al., 2014). The RewP studied in that study, has been suggested to be generated in the ACC (Gehring, 2002). This finding is especially relevant as reward processing and mesocorticolimbic pathway (i.e. a circuitry that connects the ventral tegmental area to other brain areas including the ACC), could be underlying apathetic behavior, at least in PD. Also in PD, apathy symptoms (measured with SAS) were associated with a diminished response to reward in the amygdala, vmPFC, striatum, and midbrain, assessed with positron emission tomography (Lawrence, Goerendt, & Brooks, 2011)

The Gap Between the Clinic and Neuroscience Research on Motivation

Just a few studies have included ECDM tasks and measures of apathy symptoms as reviewed at the beginning of this chapter (and in Chapter 3) and even fewer have paired neuroimaging techniques with these two outcome measures (ECDM tasks and symptoms). One study found decreased connectivity between the ACC and the supplementary motor area in relation to apathy symptoms (measured by the LARS) (Bonnelle, Manohar, Behrens, & Husain, 2015). Table 2.3 presents some of the results from a literature review by Levy and Dubois (2006) that proposes apathy as a dysfunction of the PFC and basal ganglia and links the three apathy domains to items of the SAS.

Currently, there is little understanding of how the cognitive and emotional domains of apathy relate to this neurobiologically-informed framework of motivation. Further, as this review demonstrates, existing studies have used different tasks, assessments, and clinical populations, making it hard to draw general conclusions. Apathy may be the result of different mechanisms across different clinical conditions. A better understanding of brain mechanisms underlying motivation might suggest novel, more targeted interventions, as well as provide the tasks or measures to assess the impact of such interventions.

Table 2.3

Behavior and brain impairments underlying apathy

Apathy domain	Behavioral	Cognitive	Emotional
Hypothesized brain areas.	mPFC (medial SFG and ventral ACC), large frontal lesions, and frontal white matter lesions.	Dorsolateral PFC, Dorsal caudate nucleus, globus pallidus and thalamic nuclei.	orbito-medial PFC.
Clinical assessment (SAS)	*"Do you put much effort into things",*	*"Do you have plans and goals for the future?"*	*"Are you indifferent to things?"*
Neuroscience assessments (task performance)	ECDM tasks Gambling tasks (reward processing)	Fluency tasks, Tower of London	

Note: Starkstein Apathy Scale, SAS; orbital frontal cortex, OFC; medial prefrontal cortex, mPFC; superior frontal gyrus, SFG; anterior cingulate cortex, ACC; effort-cost decision making, ECDM; prefrontal cortex, PFC. Some of this information was taken from (R. Levy & Dubois, 2006).

Motivation in Older Adults.

Apathy is prevalent in several neurological and psychiatric disorders. In the elderly, apathy is linked to cognitive decline, delirium, frailty, and higher mortality (Hölttä et al., 2012; Semprini et al., 2012). Evidence from a recent meta-analysis and a longitudinal study over nine years involving 381 participants suggests that apathy may also be an early marker of increased risk of incident dementia (Bock et al., 2020; Willem van Dalen et al., 2018). Apathy is also part of the neurobehavioral disturbances seen in chronic medical conditions that affect the brain, such as Human Immunodeficiency Virus (HIV) infection. It is estimated that apathy affects around 30 to 40% of people living with HIV (Castellon, Hinkin, Wood, & Yarema, 1998; Reekum, Stuss, & Ostrander, 2005) and apathy is linked to dependence in activities of daily living (Kamat et al.,

2012), medication nonadherence (Barclay et al., 2007) and poor mental and physical health-related quality of life (Kamat, Woods, Cameron, Iudicello, & HIV Neurobehavioral Research Program (HNRP) Group, 2016).

The studies presented in this thesis were conducted in HIV+ older people or in community-dwelling older adults. In the following sections, I will first describe some of the more common brain changes associated with aging and summarize the current findings on the neural correlates of apathy in older adults. Then I will provide a brief overview of HIV, including its effects on the brain.

Neural Correlates of Apathy in Older Adults

Aging is considered a risk factor for some health conditions like frailty, dementia, and progression of chronic diseases, especially in sedentary older adults (Merchant, Morley, & Izquierdo, 2021). Brain changes occur in healthy aging, such as changes in grey and white matter volume, and decreased major white matter tract connectivity predominantly in the anterior and superior cortical regions (Samanez-Larkin & Knutson, 2015). There is also some evidence suggesting age-related changes at the neurochemical level, such as decreased dopamine receptors in the PFC and striatum (Bäckman, Lindenberger, Li, & Nyberg, 2010; Klostermann, Braskie, Landau, O'Neil, & Jagust, 2012).

A recent systematic review on neuroimaging studies and self-reported apathy in older adults found that apathy across all studies was more consistently associated with neuroanatomical abnormalities of the ACC and OFC. Other findings included decreased resting-state functional connectivity within and between the anterior insula, ACC, caudate nucleus, thalamus, amygdala, and posterior parietal cortex (Pimontel, Kanellopoulos, & Gunning, 2020).

Evidence from other studies suggests that apathy in older people may also be linked to decreased grey matter volume of the ACC and deep white matter lesions (Lavretsky, Ballmaier, Pham, Toga, & Kumar, 2007; Yao et al., 2009).

Human Immunodeficiency Virus.

HIV was first recognized in the USA in 1981. If left untreated, HIV infection can progress to acquired immunodeficiency syndrome (AIDS) which is the most advanced stage of HIV infection (Klimas, Koneru, & Fletcher, 2008). Before effective treatments became available in 1996 (i.e. combination of antiretroviral therapy (cART)), HIV was considered a fatal disease. Currently with early diagnosis and effective treatment HIV is now considered a chronic health condition. HIV is a type of lentivirus that enters the central nervous system (CNS) by targeting CD4 T-lymphocytes, also known as CD4 T-cells, a type of white blood cell that regulates the immune response (Kramer-Hämmerle, Rothenaigner, Wolff, Bell, & Brack-Werner, 2005; Zhu & Paul, 2008). The structure of the virus is very complex, in the following sections the replication virus cycle and the effects of the virus in the brain will be briefly summarized as well as the current state of the literature regarding apathy in patients living with chronic HIV infection.

The entry of HIV into the CNS system occurs through direct contact with CD4 T-cells and the HIV surface (glycoprotein 120 (gp120). Other immune cells like monocytes and macrophages that carry chemokine receptors (CCR5 or CXCR4) can also bind to gp120 and become infected. The binding of the virus with these receptors allows the entry of HIV into the host cell; once inside, the core of the virus (capsid) disintegrates and releases its viral RNA. Through a DNA polymerase enzyme (reverse transcriptase), the viral RNA is transformed into DNA which is transported and integrated into the nucleus of the host cell. Once in the nucleus,

viral transcription is initiated (activated by transcription factors) and results in new viral RNA, used to make new viral proteins. The new viral RNA and viral proteins move to the surface of the host cell and form new immature HIV forms that will undergo a maturation process and become a mature virion that can infect new cells (Eggers et al., 2017; González-Scarano & Martín-García, 2005; Klimas et al., 2008; Kramer-Hämmerle et al., 2005).

cART combines different antiretroviral drugs to suppress viral replication at different stages of the replication cycle, which allows patients to live longer and manage HIV as a chronic illness.

Effects of HIV on the Brain.

Prior to antiretroviral therapy, the prevalence of neurological symptoms in HIV-infected patients was as high as 30%, with cognitive impairment the most common. HIV-associated neurocognitive disorders (HAND) can be classified as asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), or HIV-associated dementia (HAD). HIV-associated dementia (HAD) includes a range of cognitive, motor, and behavioral symptoms that generally occur in later stages of untreated HIV infection, in those with high plasma viral loads. Fortunately, highly active antiretroviral therapy (HAART) is effective at suppressing viral replication. The introduction of HAART was followed by a substantial reduction in the incidence of HAD (Childs et al., 1999; González-Scarano & Martín-García, 2005), although milder forms of HAND are still frequent.

This observation, as well as findings from studies in animal models and autopsies, make clear that HIV infection directly affects the brain. As mentioned, HIV primarily targets CD4+T cells but also monocytes and macrophages. HIV enters the CNS likely by infected CD4+T cells

and monocytes that migrate through the blood brain barrier (BBB) and to the CNS. While there is no evidence that HIV directly infects neurons, it affects them by infecting other cells that are essential for CNS function, such as macrophages and microglia which can also replicate the virus after infection. These in turn can release viral proteins (Tat and gp120), and neurotoxic factors that contribute to the progression of the infection in the CNS, and with time can induce a cascade of toxic effects in the brain that trigger neuroinflammation (Achmin, Wamd, Miners, & Wilwy, 1994; González-Scarano & Martín-García, 2005; Wallet et al., 2019). In addition, astrocytes, a type of glial cell that provides neuronal support and regulates neuronal communication and BBB flow, can also be affected by HIV, leading to loss of astrocyte function and brain homeostasis (González-Scarano & Martín-García, 2005; McIntosh, Rosselli, Uddin, & Antoni, 2015a). In sum, while HIV does not directly infect neurons, the effects of HIV on the brain are believed to be related to the release of viral proteins, the production of cytokines, and oxidative stress (e.g. triggered by nitric oxide release from infected macrophages and microglia) that can progress to neuronal injury.

In addition to these effects of the virus on the brain, other factors, like the earlier appearance of age-related conditions such as cerebrovascular disease, neurotoxic effects of medication, the stigma associated with having HIV, and mental health symptoms (among the most prevalent: depression and apathy) can also take a toll on the health of individuals living with chronic HIV (Brew, Crowe, Landay, Cysique, & Guillemin, 2009; Cysique & Brew, 2019; Kramer-Hämmerle et al., 2005; Lam, Mayo, Scott, Brouillette, & Fellows, 2019; Mayo et al., 2020). Thus, in persons taking antiretroviral therapy, there are likely multiple factors contributing to worsening cognition (Antinori et al., 2007; Heaton et al., 2010; Walker & Brown,

2018). Understanding the pathophysiology of HAND in the cART era remains an active research challenge.

Recent studies using neuroimaging techniques have shown smaller volumes of the thalamus, brainstem, globus pallidus, caudate nucleus and putamen in HIV+ individuals taking antiretrovirals compared to healthy controls (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Boban, Thurnher, & Kozic, 2021; Sanford et al., 2017; Sanford, Fellows, Ances, & Collins, 2018). Reduced volume of the thalamus in well-treated HIV individuals has further been linked to individual differences in cognition (Cruz et al., 2021). Changes in cortical thickness have also been reported. A decrease in cortical thickness in the OFC, cingulate, motor, and sensory cortex, and temporal and frontal lobes, has also been shown in HIV + individuals taking antiretrovirals compared to healthy controls (Kallianpur et al., 2012; Sanford et al., 2017).

Neural Correlates of Apathy in HIV

Little is known about the neural mechanisms of apathy in HIV. Specifically, it is unclear whether apathy is a direct effect of the infection on brain function, a complication of HIV or its treatment, or the result of a co-morbidity. The presence of the virus in the basal ganglia and frontal circuits has been linked to apathy in HIV, since apathy is theorized as a disruption of these areas (see Table 2.3) and the virus is also found in greater concentrations in the basal ganglia (McIntosh, Rosselli, Uddin, & Antoni, 2015).

There are currently only three studies, all with small samples sizes, investigating brain correlates of apathy in people with treated HIV. In these studies, a decreased volume of the NAcc (R. H. Paul et al., 2005) and brain white matter abnormalities (Hoare et al., 2010; Kamat et al., 2014) were linked to more apathy symptoms. CD4 cell count seems not to be strongly

related to apathy severity in treated HIV, although there are some findings linking apathy to HIV disease duration (McIntosh et al., 2015; R. Paul et al., 2005).

Specific Aims of Thesis Research

The previous chapter described the contributions of effort and reward processes to motivation and emphasized the gap between the clinic and research in neuroscience in relation to motivation. Bridging this gap will contribute to the understanding of the construct of motivation and may lead to new approaches to the diagnosis of apathy in the clinic.

The specific aims of this thesis are:

1) To estimate the extent to which the subjective cost of effort measured with an ECDM task is associated with self-reported real-world motivation in older people with well-controlled HIV infection.

2) To estimate the extent to which the subjective cost of effort measured with an ECDM task is associated with self-reported real-world motivation in community-dwelling older adults.

3) To contribute evidence for the convergent validity of two common ECDM tasks as laboratory measures related to self-reported real-world motivation.

4) To estimate the extent of the relationship between two evoked related potentials elicited by feedback in a guessing task and self-reported real-world motivation in older people with well-controlled HIV infection.

Three studies were designed to address these aims. The first and second studies focused on the effort-cost decision making stage of goal-directed behavior and the third study focused on the consummatory phase of goal-directed behavior, i.e. the interaction with the goal. The first study tested a novel ECDM task in participants with well-controlled HIV, drawn from a longitudinal study of brain health in HIV (Brain Health Now; BHN project (Chapter 3). The second study was conducted in a sample of community-dwelling older adults. This study tested

whether the results of the first study generalized to older people without HIV and also tested the convergent validity of two common ECDM tasks. This study also piloted a novel intrinsic motivation task (Chapter 4). The last study focused on two evoked related potentials recorded during feedback presentation using electrophysiology in a separate sample, also drawn from the BHN cohort. This study tested the relationship between EEG markers of feedback processing and self-reported measures of motivation (Chapter 5).

All three studies used items from the Starkstein Apathy Scale as one of the measures of self-reported motivation. These items were selected using Rasch analysis. Over the course of this research the Rasch analysis evolved, and a different subset of items were used throughout the three studies (see Appendix III; Figure 7.3). To help the reader we will use Starkstein Apathy Scale-Rasch (SAS-R) or self-reported motivation to refer to the items derived from the SAS; although the actual items varied.

Chapter 3

Does Effort-Cost Decision-Making Relate to Real-World Motivation in People Living with HIV?

Preface

Motivation has been primarily measured with self-reported questionnaires and clinician ratings, which may have limited generalizability to broader research settings. For instance, it is difficult to compare self-reported questionnaires with animal models of motivation. Cognitive neuroscience offers a framework that separates motivation into component constructs that may be more readily linked to neural circuits, but it remains to be established how these putative components apply in the clinic. Effort cost decision making (ECDM) focuses on the subjective cost of effort, a construct with face validity to real-world motivation. The study reported here sought evidence for the validity of a laboratory ECDM task in relation to motivation in older people living with HIV.

We chose HIV as the population of study because of the high prevalence of motivational symptoms among individuals living with HIV, among a wide range of other mental health and neurological symptoms including fatigue, depression, and mild cognitive impairment. This study is one of a few conducted in a clinical sample that attempted to test the specificity of the hypothesized relationship between ECDM and motivation, using a portfolio of brain health measures. This project examined the extent to which the subjective cost of cognitive and

physical (handgrip) effort measured with an ECDM task was associated with self-reported measures of motivation. Motivation was assessed with items derived from a widely-used apathy questionnaire that asks about beliefs and actions related to motivation, as well as by the self-reported time spent on goal-directed activities per week. We also examined the specificity of the hypothesized relationships by including other brain health constructs: cognition, depression, anxiety, and vitality.

Does Effort-Cost Decision-Making Relate to Real-World Motivation in People Living with HIV?

Gloria Castaneda[1], Ana Lucia Fernandez Cruz[1], Marcus Sefranek[1], Yvonne H.C. Yau[1], Marie-Josée Brouillette[2], Nancy E. Mayo[3], and Lesley K Fellows[1].

[1]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University.

[2]Department of Psychiatry, Faculty of Medicine, McGill University

[3]Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Canada.

Abstract

Introduction: Low motivation is frequent in older people with HIV, yet poorly understood. Effort-cost decision-making (ECDM) tasks assess aspects of motivated behavior, with evidence for a relationship with clinical symptoms in schizophrenia but have not been applied in HIV. Here we sought evidence for a relationship between the subjective cost of effort measured with an ECDM task and self-reported motivation in a sample of 80 middle-aged and older people with well-controlled HIV infection. Methods: Participants were drawn from an ongoing Canadian cohort study of brain health. Self-report measures of motivation, cognition, depression, anxiety, and vitality, as well as time spent on personally meaningful activities were gathered. Results: We found no relationship between ECDM and motivation. However, those willing to accept higher effort in the ECDM also reported more hours spent on meaningful activities. Conclusions: A more fine-grained approach to the complex construct of motivation is needed. ECDM shows promise as an indicator of real-world brain health challenges, but a full understanding of its potential will require refining motivation assessment.

Keywords: reward, effort, apathy, motivation, measurement, human.

Introduction

Motivation is a key determinant of goal-directed behavior (Mann, 1990; Marin & Wilkosz, 2005a). It is a multi-faceted construct, implicated in activating, directing and sustaining pursuit of a goal (Strombach et al., 2016). In the clinic, low motivation is considered a cardinal feature of apathy (Marin & Wilkosz, 2005a). Low motivation is prevalent in chronic conditions that affect the brain, including psychiatric conditions, neurodegenerative disorders, and systemic conditions common in older age. Treated human immunodeficiency virus (HIV) infection is one such chronic condition. As people are living longer with HIV thanks to antiretroviral treatment, the toll on mental and neurological health is of growing concern (Heaton et al., 2010). Low motivation in HIV is prevalent, as is mild cognitive impairment, depression, anxiety, and reduced vitality (i.e., fatigue), (Heaton et al., 2010; Kamat et al., 2016; Kaur, Dendukuri, Fellows, Brouillette, & Mayo, 2019). Apathy has been linked to dependence in activities of daily living (Kamat et al., 2012), medication nonadherence (Barclay et al., 2007) and poor mental and physical health-related quality of life in people with HIV (Kamat et al., 2016).

Despite the prevalence and impact of low motivation, little is known about the underlying mechanisms. Relatedly, there is little consensus on how best to identify or treat it. While a descriptive approach to diagnosis relying on clinician interview or self-report has dominated the field so far, there is emerging interest in understanding motivation within a neurobiological framework. Drawing on behavioral economics and decision neuroscience, specific component processes of motivation have been proposed and laboratory tasks have been developed to assess them. The subjective discount of effort, the value of a reward discounted by the effort required to obtain it, typically assessed by asking participants to make

choices about whether they are willing to complete effortful actions (such as exerting a physical force or completing a cognitively difficulty task) in exchange for monetary rewards, is one candidate component process.

Versions of effort-cost decision-making (ECDM) tasks have been tested in healthy people and in some clinical populations, including schizophrenia, major depressive disorder, and Parkinson's Disease (PD). Higher subjective costs of effort have been consistently reported in clinical compared to healthy samples (Chong, Bonnelle, & Husain, 2016; Chong et al., 2015; Culbreth, Moran, & Barch, 2017; Horan et al., 2015; Huang et al., 2016; Le Bouc et al., 2016; Zénon et al., 2016). Whether ECDM performance relates to clinical symptoms in these samples is less clear. The most-studied condition is schizophrenia, with a focus on so-called negative symptoms, which include anhedonia, asociality, blunted affect, alogia and lack of motivation (Blanchard & Cohen, 2006; Millana et al., 2014). A recent review of ECDM in schizophrenia found mixed results: 10 studies reported an association between higher negative symptoms and lower proportion of ECDM offers accepted while 5 studies did not find associations between ECDM performance and negative symptoms (Culbreth et al., 2018). In a sample of participants with depression, two studies (Hershenberg et al., 2016; Treadway, Bossaller, et al., 2012) found that worse depression was linked to a paradoxical willingness to accept higher-effort ECDM offers.

One reason for the mixed results could be that the neurobiological mechanisms underlying the variation in subjective cost of effort are different across disorders (Culbreth et al., 2018). Computational modeling of ECDM data can disentangle the two elements that presumably influence ECDM: reward sensitivity and effort sensitivity, which could identify

more distinct phenotypes underlying low motivation. Using this method, apathy severity was shown to be associated with greater sensitivity to effort in one sample of healthy individuals (Bonnelle, Manohar, et al., 2015; Bonnelle, Veromann, et al., 2015), and to decreased reward sensitivity in a study of PD patients taking dopaminergic medication (Le Bouc et al., 2016).

Beyond the schizophrenia literature, there are few studies that have investigated the relation between self-reported motivation or apathy and ECDM or that have tested the specificity of such a relationship in other brain health constructs such as depression, anxiety, poor cognitive performance and low vitality, which often co-occur with low motivation and might plausibly influence ECDM. Larger studies in diverse clinical samples are needed to clarify the relationship between ECDM and clinical symptoms, as a starting point for applying decision neuroscience to better understand, diagnose, and perhaps treat low motivation.

The primary objective of this study is to estimate the extent to which the subjective cost of effort measured by the proportion of accepted offers in an ECDM task is associated with self-reported motivation in a sample of older people with well-controlled HIV infection. A secondary objective is to contribute evidence for the specificity of this hypothesized relationship by estimating the extent to which the subjective cost of effort measured by an ECDM task is associated with other brain health constructs including cognition, depression, anxiety, vitality, and self-reported time spent doing meaningful real-world activities.

Methods

Participants

A sample of older participants was recruited from the Positive Brain Health Now cohort (BHN), a Canadian longitudinal study of brain health in middle-aged and older people with combination antiretroviral therapy (cART)-treated HIV. The BHN study protocol has been published (Mayo, Brouillette, Fellows, & Investigators, 2016). 117 sequential BHN participants were approached for this sub-study at the time of a routine follow-up visit for the main study at one site in Montreal, of whom 29 declined and 88 accepted. Seven of those who accepted subsequently rescheduled their main study visits and were not available for testing. One participant could not complete testing due to an equipment problem. Thus, data from 80 participants were available for analysis. The 29 who refused participation in this sub-study nonetheless were characterized on available BHN data, to assess selection bias.

Inclusion criteria for the main study were age 35 years or older, HIV infection for at least one year, able to communicate in French or English. Exclusion criteria included dementia that precluded capacity to consent, life expectancy of <3 years, other neurological disorder likely to affect cognition, current substance use disorder or severe substance use disorder within the past 12 months. There were no additional inclusion or exclusion criteria for this sub-study. The main study and sub-study were both approved by the research ethics board of the McGill University Health Center. All study participants were compensated for their time and those included in this sub-study received an additional amount that they were told depended on their choices in the task. The total compensation for participating in the sub-study was 15$CDN.

Self-Report Measures

Motivation

Items 1, 2, 4, 6, 7, and 8 of the Starkstein Apathy Scale (AS) were used to assess motivation (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992). These six questions were chosen based on Rasch analysis (Smith, 2004) of the original 14 AS items, in a separate sample. For the purposes of presentation, logit scores were transformed to a 0-100 scale with higher scores indicating more motivation. Data from a screening version of 3-items of the AS, scored using the same method, were available for refusers.

Cognitive Symptoms

The Communicating Cognitive Concerns Questionnaire (C3Q) (Askari, Fellows, Brouillette, & Mayo, 2020) is an 18-item self-report questionnaire targeting specific cognitive concerns relevant to people with HIV. The C3Q assesses memory, attention, executive function and language. The extent to which these items fit a linear hierarchy and form a measure has been tested using Rasch analysis and the validity of summing across the ordinal response scale (frequently, sometimes, and rarely using values of 0, 1 and 2) demonstrated. The total score, ranges from 0 to 36, with higher values indicating better cognition (i.e., fewer cognitive symptoms).

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was used to assess anxiety and depression symptoms. This is a 14-item scale, 7 items assessing anxiety and 7 items assessing depression. The linear hierarchy of the items has been tested and the validity of summing the ordinal response options (0 to 3) demonstrated (Pallant & Tennant, 2007). To

facilitate the comparison between the HADS and the rest of the questionnaires used in this study, the original scale was reverse so that higher scores indicated better mood (i.e. fewer symptoms).

Vitality

The RAND-36 measure of health-related quality of life Energy/Fatigue subscale (Hays & Morales 2001) was used to assess vitality. Final scores range from 0 to 100 scale with 100 being a more favorable health state; that is more vitality. The nine items of this subscale are answered along a 5-point ordinal scale, ranging from "All the time" to "None of the time".

Meaningful Activity

Participants were asked to report the number of hours they spent in a typical week doing personally meaningful leisure activities: reading, checking their email, surfing the internet or other computer activities, games, doing crafts or hobbies, and any other leisure-time activities, if specified. Only activities carried out for more than 20 min a week were included. This list is drawn from the health outcomes-rehabilitation literature, based on the Community Healthy Activities Model Program for Seniors (CHAMPS) measure (Stewart et al., 2001). In the present study, this was used as an indicator of engagement in real-world, personally meaningful self-directed behaviors. Time spent on paid work was not included.

Performance measures

Cognitive Performance

The Brief Cognitive Ability Measure (B-CAM) (M. J. Brouillette et al., 2015) includes a series of cognitive tests assessing, episodic memory (verbal recall), attention (Corsi block test), and executive function (Flanker task, Trail-Making Task-B, phonemic verbal fluency). The

continuous scores in the items were converted into multiple categories that represented the item-distribution and the granularity of the underlying latent trait (cognitive ability). The items were shown, using Rasch analysis, that they can be combined to provide a global measure of cognitive ability with a total score ranging from 0-41 with higher scores indicating better cognitive performance.

Effort-Cost Decision Making task

After completion of the questionnaires, participants were seated in front of a computer running Cogent 2000 (www.vislab.ucl.ac.uk) implemented for MATLAB. At the beginning of each session, the participant's maximum voluntary contraction (MVC) was estimated by having them squeeze a hand dynamometer with their dominant hand as hard as they could for a period of 5 seconds, twice. The MVC was the average of these two values. This was labelled "100% force". They were next asked to exert about 50% of that force and hold it for 20 seconds, to familiarize themselves with the subjective experience of the lower force levels that would be required as the physical effort in the ECDM task.

Participants were next asked to cancel out all the letter "e"'s on a page of text composed of random letter sequences as quickly as they could for two minutes. The 20% mental effort level corresponded to the total number of lines of text they canceled during these two minutes. Participants were then shown the number of lines corresponding to each of the five mental effort levels that would feature in the ECDM task.

After these effort calibration procedures, the ECDM paradigm was administered. This was a slightly modified version of the task used in Study 2 in (Bonnelle, Veromann, et al., 2015). Participants were asked to make hypothetical choices between different levels of effort for

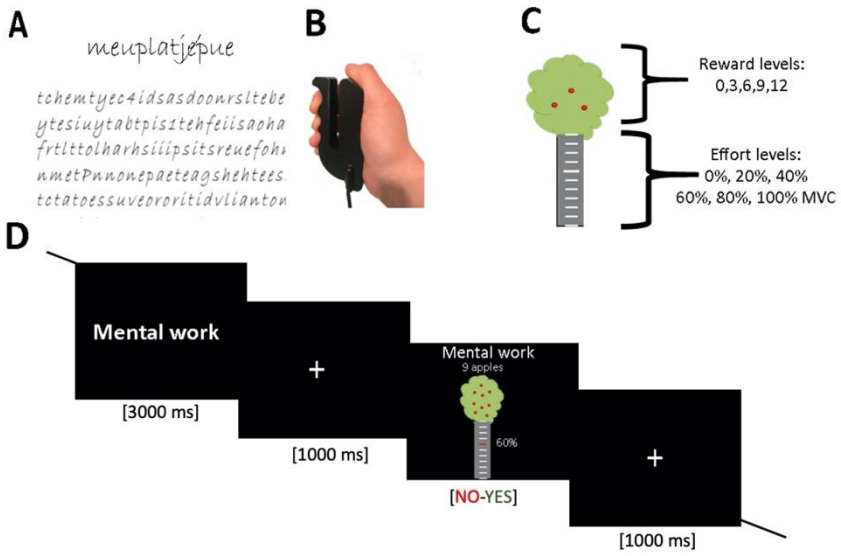
different amounts of monetary reward. Each trial presented an apple tree that showed the reward at stake (number of apples) and the effort level required to gain the reward (trunk height), see Illustration 1. There were six different reward levels (i.e. 0,1, 3, 6, 9, and 12 apples), and six effort levels (i.e. 0%, 20%, 40%, 60%, 80% and 100% MVC). Consequently, there were 36 possible combinations of effort and reward, each appearing once during the six blocks of the task for a total of 216 trials.

Three blocks involved mental effort (crossing out the letter "e") and three blocks involved physical effort (MVC). The type of effort required was indicated at the beginning of each block and at the top of the screen on each trial. Participants decided if they would be willing to make the required effort in order to win the presented reward, responding "yes" or "no" by pressing the right (yes) or left (no) arrow key of a standard keyboard. Responses were self-paced.

Participants were instructed that at the end of the game, one of the trials would be chosen at random, and they would have to play out the selected choice to earn a real monetary reward of up to 15$, which would be added to the amount of 40$, an amount they receive for their BHN visit. Thus, they were encouraged to make each choice as though it was "for real". Four practice trials, two involving mental effort and two involving physical effort preceded the main task. After the 4 practice trials, participants were asked to explain the task in their own words. If needed, the instructions and practice trials were repeated until the task was understood.

Figure 3.1

Figure of the ECDM task



Note: (A). Example of a section of the mental effort worksheet. (B). Handgrip participants used to exert force in the physical force. (C) Summary of the 36 possible effort-reward combinations and an example of the apple tree graphic used to convey these combinations. (D). Example trial of a mental effort block. Participants were presented with the type of block ("mental work" or "physical work") for 3000 ms, followed by a fixation cross for 1000 ms, and the presentation of the choice where participants accepted or rejected the offer. Participants declined offers ("NO") by pressing the left arrow key in a computer keyboard and accepted offers ("YES") by pressing the right arrow key. Modified task version of (Bonnelle, Veromann, et al., 2015).

Statistical Analysis

To characterize the sample, means, standard deviations, and proportions were used. The distribution of participants and refusers across study variables was compared using t-tests for the demographic variables and logistic regressions for brain health measures adjusted for sex and age. Two of these measures (i.e. cognitive symptoms and depression) were used

categorically to better fit the models. The primary outcome of the ECDM task was the proportion of accepted offers across all six effort and six reward levels, initially calculated for the mental and physical tasks separately. To estimate the strength of the relationship between proportion of accepted offers in the ECDM task and self-reported brain health measures, spearman rho correlations were calculated.

In a secondary exploratory analysis, we used computational modeling to estimate the influence of effort and reward on participants' choices during the ECDM task. This was inspired by prior evidence suggesting that there might be distinct effects of neurological conditions on reward vs. effort sensitivity. Specifically, apathetic healthy participants were found to have higher effort sensitivity with intact reward sensitivity compared to non-apathetic participants (Bonnelle, Manohar, et al., 2015).

The influence of effort and reward on choice was estimated using an approach from previous work (Bonnelle, Manohar, et al., 2015) by fitting the choices of each participant to a logistic regression model of choice probability with a softmax function, see Equation 1:

$$\mathrm{P(yes)} = \frac{1}{(1 + \exp\left(\mathrm{b_r\ x\ Reward} + \mathrm{b_e\ x\ Effort} + \ \mathrm{b0}\right)}$$

where P(yes) is the probability of accepting an offer, br reflects the sensitivity to reward, be the sensitivity to effort and b0 is the response bias (i.e. selection of a "no" response). Model parameters were optimized by minimizing the negative log likelihood. This model has been applied in previous studies using similar ECDM paradigms (Bonnelle, Manohar, et al., 2015; Bonnelle, Veromann, et al., 2015). Spearman rho correlations were conducted to explored whether these three model parameters relate to measures of brain health in people with HIV. This relationship was also tested for each brain health variable individually using linear

regression. The results of the linear regression are not presented in this paper as they did not add any new information.

Results

Data on 80 participants were included in the analysis: 68 men (mean [*M*] = 56.80, standard deviation [*SD*]= 8.30), and 12 women, (*M*=53.11, *SD*= 5.54), as well as data available from the parent study on the 29 refusers (*M*= 56.49, *SD*=7.18). Of all participants 91% were virologically supressed (≤ 50 copies/mL), and 83% were taking antiretrovirals at the moment of the study. Table 3.1 shows the demographic and HIV-related clinical characteristics of the participants and refusers. Those who participated in the study did not differ from those who refused on any of these variables.

Table 3.1

Demographic and clinical characteristics of the study sample and refusers

Characteristics	Study sample N=80			Refusers N=29			*t*(107)	*95% CI*	
	M OR %	*SD*	*Median*	*M OR %*	*SD*	*Median*		*LL*	*UL*
Age (Years)	56.25	8.02	55.48	56.49	7.18	56.93	55.09	-3.112	3.603
Women	15%			14%					
Men	85%			86%					
Education (Years)	13.94	2.65	13.00	13.79	2.45	13.00	53.65 [a]	-1.277	0.964
Estimated duration of HIV infection (Years)	19.67	7.29	20.97	19.72	9.00	18.06	42.06	-3.291	3.395
Current CD4 (Cells/µL)	646.81	258.43	621.00	641.58	354.50	569.00	39.31	-128.426	117.961
IQR			488-798			421-802			
0-199	1%			10%					
200-500	25%			24%					
> 500	74%			66%					
Nadir CD4 cell count (Cells/µL)	209.75	171.40	179.00	230.79	207.30	154.00	42.67	-56.941	99.027
IQR			88-272			79-320			

Note: IQR= Inter-quartile range.

[a] *t*(106)

Table 3.2 shows the characteristics of the study sample and refusers on brain health constructs including the screening measure for motivation and other self-reported brain health measures as well as cognitive performance assessed by a brief computerized battery. There were no differences between refusers and participants on brain health constructs as shown by the confidence interval around the odds ratio which included the null value of 1.0.

Table 3.2

Characteristics of the study sample and refusers on brain health constructs

Measure	Study sample N=80			Refusers N=29			*OR*	95% *CI*	
	n	*M*	*SD*	*n*	*M*	*SD*		*LL*	*UL*
Self-reported									
SAS-R screening (Motivation) [0-100][a]	80	66.83	27.49	29	59.03	26.59	0.990	0.974	1.005
SAS-R (Motivation) [0-100][b]	80	74.36	21.64						
C3Q (Cognitive symptoms) [0-36]	78	25.47	8.27	28	25.46	7.81			
<23 vs 23-30							2.037	0.701	5.919
>30 vs <23							0.727	0.232	2.280
HADS-D (Depression) [0-21][c]	80	15.98	3.92	29	17.00	3.27			
<=14 vs 19-21							0.331	0.093	1.178
15-18 vs 19-21							1.648	0.613	4.430
HADS-A (Anxiety) [0-21][c]	80	14.40	4.36	29	14.27	3.63	0.992	0.895	1.099
RAND-36 (Vitality) [0-100]	80	55.80	23.06	29	56.72	20.58	1.002	0.983	1.021
Meaningful activity [hrs/week]	80	38.26	29.58	29	28.13	25.41	0.985	0.968	1.002
Performance measure									
B-CAM (Cognitive performance) [0-35]	80	21.05	4.54	29	20.61	4.85	0.978	0.888	1.078

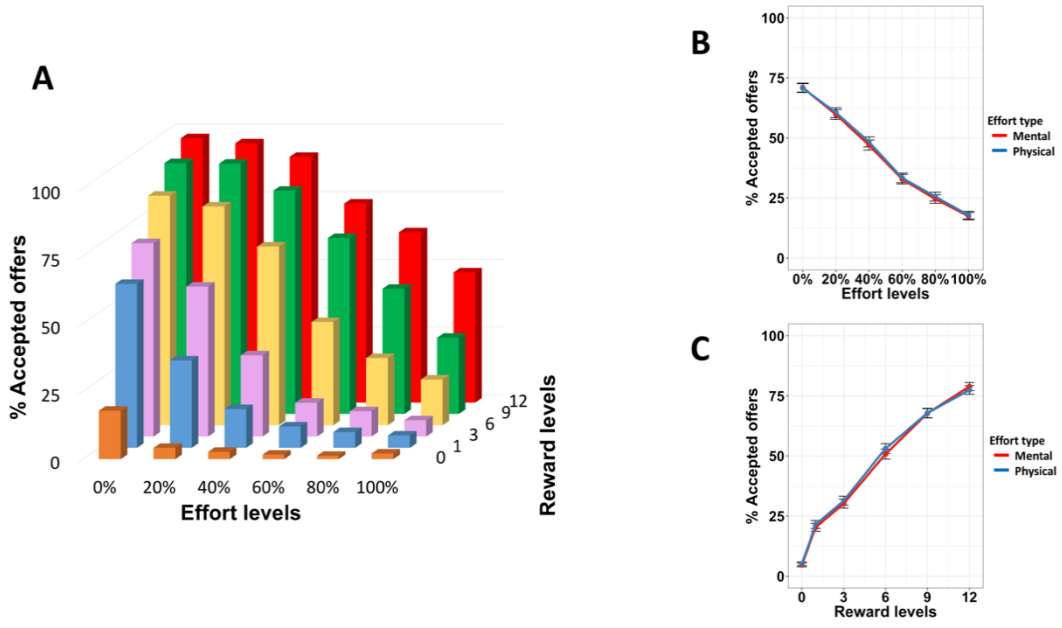
Note: SAS-R= Starkstein Apathy Scale-Rasch; C3Q= Communicating Cognitive Concerns Questionnaire; HADS-D= Hospital Anxiety and Depressive Scale-Depression Score; HADS-A= Hospital Anxiety and Depressive Scale-Anxiety Score; B-CAM= Brief Cognitive Ability Measure.

EDCM task performance is shown in Illustration 2. The mean proportion of accepted offers are displayed as a function of effort and reward levels. The mean proportion of accepted offers across the entire task was 42.44% (SD=16.20). There were significant main effects of both effort (F (5,395)=164.6, p<.001) and reward (F(5,395)=244.4, p<.001) on acceptance, in the expected directions (i.e. trials offering lower effort or higher reward were more likely to be accepted). There was also a significant effort by reward interaction (F(25,1975)=29.38, p<.001). As shown in panels 2B and 2C of Illustration 2, there was no difference in the influence of either

reward or effort on the mean proportion of accepted offers between the two types of effort. The overall proportion of mental effort trials accepted was 42.11%, SD= 15.85 and of physical effort trials was 42.75%, SD = 17.08; (t (79) = -0.934, p=.353). All subsequent analyses were collapsed across effort type.

Figure 3.2

ECDM Task Performance



Note: (A). Mean percentage of offers accepted for each of the 36 conditions (6 effort x 6 reward levels). Panels B and C show mean percentage of offers accepted by effort level (B) or reward level (C) with mental and physical effort trials shown separately.

We entered participants' responses from the task (i.e. to accept or reject an offer) into the choice probability model shown in Equation 1 to estimate beta weights for effort sensitivity,

reward sensitivity and response bias. Table 3.3 shows the results of this analysis. Effort and Reward variables were associated with the probability of accept an offer in the ECDM.

Table 3.3

Results of the choice probability model predicting ECDM choices

ECDM Outcome	Variables	Parameter Estimate (b)	M	SE	T-statistic
Probability of accepting an offer in the ECDM task	Effort	Effort sensitivity	-0.85 [a]	0.06	14.17 [b]
	Reward	Reward sensitivity	0.93 [a]	0.07	13.29 [b]
		Response bias	-1.22 [a]	0.32	3.81 [b]

[a] For easier visualization, the sign was transformed in all 3 parameters, so that be had a negative sign and br a positive sign.

[b] T-statistic is equal to β/SE and is equivalent to a t test. A value of ± 1.96 is considered significant.

Table 3.4 shows the relationships between the self-reported brain health measures (Spearman's rho) as well as overall cognitive performance assessed with the B-CAM. As expected, the brain health measures were correlated, with the strongest correlations between HADS-D, HADS-A and RAND-36. That is, fewer symptoms of depression were linked to fewer symptoms of anxiety and higher vitality. Motivation, measured with SAS-R, was weakly correlated with all other brain health measures except hours of meaningful activity and B-CAM. That is, higher motivation was linked to fewer cognitive symptoms and fewer symptoms of depression and anxiety as well as to vitality (fewer symptoms of fatigue). Amongst all the brain health measures, only cognitive performance showed a relationship with meaningful activity.

Table 3.4

Correlation coefficient values among the brain health constructs

Brain health measures	SAS-R	C3Q	HADS-D	HADS-A	RAND-36	Meaningful activity	B-CAM
Self-reported							
1. SAS-R[a]	—						
2. C3Q	**0.35** [0.126, 0.532]	—					
3. HADS-D[b]	**0.39** [0.177, 0.566]	**0.52** [0.324, 0.674]	—				
4. HADS-A[b]	**0.33** [0.115, 0.519]	**0.56** [0.371, 0.705]	**0.64** [0.467, 0.760]	—			
5. RAND-36	**0.39** [0.177, 0.566]	**0.52** [0.323, 0.674]	**0.60** [0.422, 0.733]	**0.65** [0.486, 0.771]	—		
6. Meaningful activity	0.10 [-0.122, 0.314]	0.08 [-0.148, 0.295]	0.15 [-0.069, 0.363]	0.12 [-0.106, 0.329]	-0.02 [-0.236, 0.203]	—	
Performance measure							
7. B-CAM	0.06 [-0.158, 0.280]	**0.45** [0.237, 0.614]	0.22 [-0.003, 0.421]	**0.27** [0.046, 0.463]	0.11 [-0.110, 0.325]	**0.28** [0.063, 0.477]	—

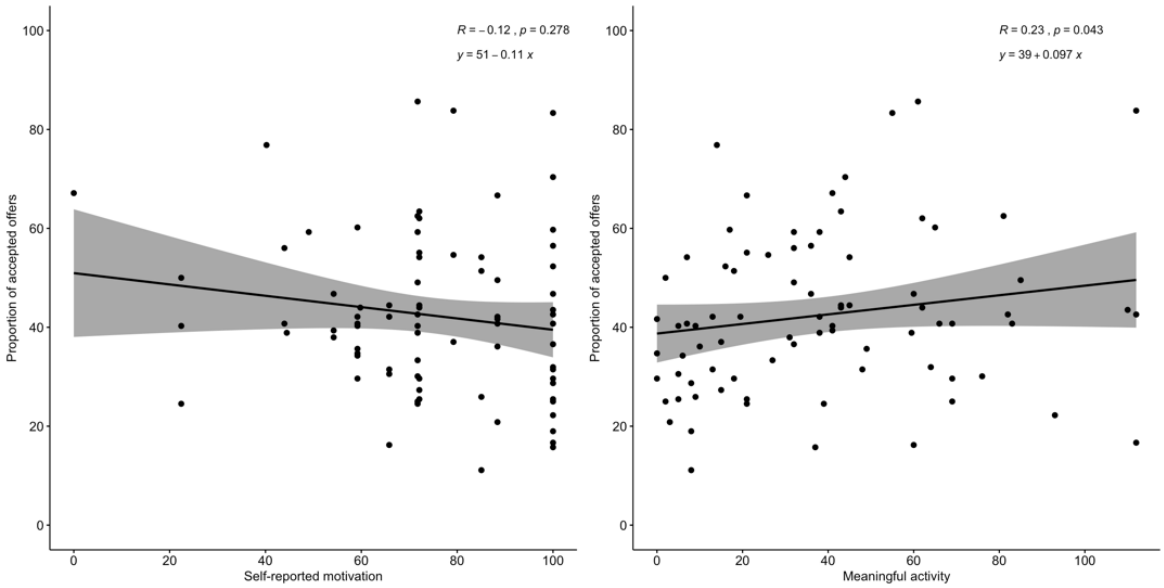
Note: SAS-R= Starkstein Apathy Scale-Rasch; C3Q= Communicating Cognitive Concerns Questionnaire; HADS-D= Hospital Anxiety and Depressive Scale-Depression Score; HADS-A= Hospital Anxiety and Depressive Scale-Anxiety Score; B-CAM= Brief Cognitive Ability Measure. Values in square brackets indicate the 95% confidence interval for each correlation.

[a] Higher scores indicate more motivation.

[b] Scores were reversed from their original score so that higher scores indicate fewer symptoms.

Figure 3.3

Scatterplots depicting the correlation between proportion of ECDM accepted offers and selected brain health measures



Note: Top right of each panel shows the spearman rho correlation coefficient and the slope of the linear regression. Shaded area displays the 95% confidence intervals.

Next, we asked whether the primary outcome of the ECDM task was related to the brain health measures. As summarized in Table 3.5, SAS-R a measure of self-reported motivation was not related to proportion of accepted offers. However, time spent on meaningful activity was positively related to proportion of offers accepted in the ECDM task. That is, participants who reported more time spent on meaningful activity (i.e. computer surfing, hobbies, etc.) also had a higher proportion of offer acceptance in the task. Illustration 3 shows the scatterplots of these relationships.

Table 3.5 also shows the Spearman's rho correlation coefficients between the secondary ECDM task outcome measure and the brain health measures. There was a correlation between

be (effort sensitivity) and b0 (response bias) and anxiety. That is, those reporting more symptoms of anxiety were more likely to accept effortful offers. There was no relation between effort sensitivity or response bias with self-reported motivation, meaningful activity or the other brain health measures and reward sensitivity was not related to any brain health measure. Reward sensitivity showed a greater numerical relationship with meaningful activity than did effort sensitivity, although the confidence interval included 0.

Table 3.5

Correlation coefficient values of brain health measures and ECDM

Brain health measures	Primary ECDM outcome measure	Secondary ECDM outcome measures		
	Proportion of offers accepted	Effort sensitivity (be)	Reward sensitivity (br)	Response bias (b0)
Self-reported				
1. SAS-R[a]	-0.12 [-0.353, 0.108]	-0.16 [-0.381, 0.076]	0.03 [-0.219, 0.268]	-0.04 [-0.264, 0.185]
2. C3Q	-0.18 [-0.421, 0.062]	-0.17 [-0.396, 0.055]	0.03 [-0.210, 0.275]	-0.08 [-0.322, 0.154]
3. HADS-D[b]	-0.06 [-0.303, 0.191]	-0.20 [-0.431, 0.025]	-0.07 [-0.292, 0.160]	0.11 [-0.124, 0.344]
4. HADS-A[b]	-0.05 [-0.284, 0.188]	**-0.27** [-0.490, -0.045]	-0.11 [-0.338, 0.114]	**0.23** [-0.016, 0.457]
5. RAND-36	-0.10 [-0.341, 0.144]	-0.21 [-0.432, 0.021]	-0.10 [-0.334, 0.129]	0.15 [-0.082, 0.386]
6. Meaningful activity	**0.23** [0.004, 0.450]	0.07 [-0.189, 0.330]	0.22 [-0.009, 0.447]	-0.03 [-0.271, 0.206]
Performance measure				
7. B-CAM	-0.13 [-0.352, 0.096]	-0.18 [-0.413, 0.048]	0.02 [-0.209, 0.251]	-0.06 [-0.289, 0.177]

Note: SAS-R= Starkstein Apathy Scale-Rasch; C3Q= Communicating Cognitive Concerns Questionnaire; HADS-D= Hospital Anxiety and Depressive Scale-Depression Score; HADS-A= Hospital Anxiety and Depressive Scale-Anxiety Score; B-CAM= Brief Cognitive Ability Measure. Values in square brackets indicate the 95% confidence interval for each correlation.

[a] Higher scores indicate more motivation.

[b] Scores were reversed from their original score so that higher scores indicate fewer symptoms.

We also explored whether brain health symptoms affected model fit, reasoning that impairments might lead to more variable ECDM choices, rather than or in addition to systematic effects on reward or effort sensitivity. Overall, there was a non-significant trend for

a relationship between model fit and self-reported motivation (Spearman r= -.188, *p*=.095) and cognitive performance (Spearman r= -.190, *p*=.091) with a better fit in participants with higher motivation and better cognitive performance.

Discussion

This study investigated whether the subjective cost of effort measured by the proportion of accepted offers in an ECDM task was associated with self-reported motivation or with other brain health constructs, in individuals with well-controlled HIV infection. Chronic HIV infection is associated with a high prevalence of mental health symptoms and mild cognitive impairment due to a variety of factors including direct effects of HIV in the brain, cerebrovascular comorbidity, aging effects and stigmatization (Mayo et al., 2020; Rubin & Maki, 2019). We expected that this heterogeneity would provide a useful test bed for studying the links between laboratory and clinical indicators of low motivation, and for testing the specificity of any such relationships. This is the first study using ECDM in a sample with HIV infection and one of the few that included measures of self-reported motivation in addition to other related brain health constructs.

Participants generally made rational choices that varied systematically with reward and effort requirements, suggesting that they understood the task. The hypothesized relationship between individual differences in the proportion of accepted offers in the ECDM task and self-reported motivation was not observed. However, ECDM task performance did relate to a measure of real-world engagement in self-directed behaviors, i.e. self-reported hours spent on personally meaningful activities in everyday life. A secondary analysis using a computational

modeling approach confirmed the lack of relationship between self-reported motivation and either effort or reward sensitivity expressed in the ECDM task. This exploratory analysis showed a relationship with anxiety severity, with less sensitivity to the cost of effort in those with worse anxiety symptoms.

While ECDM tasks have face validity as indicators of motivation, the literature linking task performance to clinical symptoms of low motivation or apathy is conflicting. Most of the existing literature shows only that ECDM performance differs between healthy and clinical samples. Several studies have investigated the relationship between ECDM and clinical symptoms of motivation, most in schizophrenia, with positive and null results reported (Culbreth et al., 2018). Two studies in PD and two in healthy individuals have also addressed this question (Bonnelle, Manohar, et al., 2015; Bonnelle, Veromann, et al., 2015; Le Bouc et al., 2016; Le Heron, Plant, et al., 2018). All 4 studies reported a link between higher apathy scores and ECDM performance. This work did not test for the specificity of this relationship, excluding participants with lower cognitive abilities and symptoms of mood disorders a priori. These studies also had small sample sizes with the attendant risk of publication bias of positive results. The findings here, in a larger sample suggest that the relationship between ECDM performance and self-reported motivation symptoms is not robust, or at least not in people with HIV. Of note, the mean proportion of accepted offers in our task appears to be similar to that observed in other studies using similar tasks, suggesting that the failure to replicate is not due to major differences in the subjective cost of effort across samples, nor to differences in the methodological details of the ECDM tasks used in this literature.

For various reasons, correlations between self-report and behavioral measures tend to be weak (Goodwin et al., 2016). The correlation is likely to be even weaker if one measure has poor reliability (Dang, King, & Inzlicht, 2020). There are two studies, in healthy individuals and schizophrenia, raising doubts about the psychometric characteristics of ECDM tasks, including a task similar to the one used here, had poor test-retest reliability and weak external validity (Horan et al., 2015; Reddy et al., 2015a). This may be part of the explanation for the findings here, as well as the low correlations reported in the existing literature, which fall between 0.3-0.6, when present. However, our findings provide some evidence for external validity for the ECDM task, showing an association between task performance and real-world engagement.

A further consideration is the validity of the self-reported motivation assessment we used. The items were selected from the widely-used Starkstein Apathy Scale (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992) based on Rasch analysis, a process that yields a semi-quantitative measure of a single construct (i.e. motivation, in this case). This modern psychometric approach should yield a more meaningful score than the full instrument, given that we found several mis-fit and redundant items in the conventional AS. The expected correlation between motivation and other self-reported brain health constructs such as vitality, cognition and depression provide some evidence for the validity of this approach to assessing self-reported motivation. However, the use of this refined version of the AS makes it difficult to relate current findings directly to the existing literature, although that literature itself uses diverse questionnaires. There is a clear need for more psychometrically and conceptually robust self-report measures of motivation to advance this line of research.

Participants also reported the time spent doing meaningful activities (e.g. computer use, hobbies, etc.). We reasoned that motivation was amongst the capacities required for engagement in such self-directed behaviors (Marin & Wilkosz, 2005b). While greater engagement in activities likely implies more motivation, less engagement could be due to difficulties in other capacities. Our finding that time spent on meaningful activities was the only measure related to cognitive performance assessed with a laboratory (computerized) measure of cognitive ability that assesses memory, attention and executive function, and the only one related to proportion of accepted offers in the laboratory ECDM task, suggests that working back from reported real-world engagement to better define the neurobiological processes that limit real-world activities in people living with HIV may be a fruitful strategy. These laboratory performance measures may be inherently more strongly linked to direct assessment of real-world "performance" (i.e. engagement) than to self-reported clinical symptoms.

People with low motivation are likely to be less willing to participate in research. A strength of the present study is that the participation rate was high, and we assessed potential selection bias by comparing those who agreed to participate in this study with those who refused. There were no substantial demographic or clinical differences between these groups. This study drew on a cohort (the BHN study) that recruited from consecutive patients at a specialized HIV clinic at a tertiary care hospital. We also characterized selection bias in the main BHN sample, finding that those who refused were generally younger and less concerned about brain health symptoms (Mayo, Brouillette, & Fellows, 2018). Thus, the sampling frame for the current study is likely to over-represent those with lower levels of motivation and worse brain health, i.e. a group for whom motivation assessment may be most clinically relevant.

In summary, we find mixed support for the claim that individual differences in subjective cost of effort as assessed by a laboratory task grounded in decision neuroscience relates to clinical symptoms of low motivation or related brain health constructs in older people living with chronic HIV infection. The observed link with real-world activities, while a small effect, merits further study. The largely null findings with respect to brain health symptoms may reflect methodological distinctions between how symptoms and performance are assessed. We suggest a need for better patient-centered outcome measures of low motivation suited to those living with HIV; these might be usefully validated against engagement in real-world activities, whether self-reported or assessed by activity monitors

Notes

We thank Melissa Vu for her assistance with recruitment and Masud Husain, Alexander Soutschek, Philippe Tobler and Todd Hare for helpful discussion in the design phase of this work and for sharing versions of the ECDM task. This work was supported by Team Grants from the Canadian Institutes of Health Research (CIHR) (TCO-125272; HAL-157987) and by the CIHR HIV Clinical Trials Network (CTN 273), a grant from the Velux Foundation with support from the Brain@McGill programme, and the Healthy Brains for Healthy Lives CFREF grant to McGill University. Authors have no conflicts of interests to declare. Data is available only to editors and reviewers upon request.

Chapter 4

Comparison of Effort-Cost Decision-Making Tasks and Their Relation to Self-Reported Motivation in Community-Dwelling Older People

Preface

In Chapter 3, I showed that meaningful activity, but not self-reported motivation (SAS-R) was positively related to the proportion of accepted offers in an ECDM paradigm in an HIV+ sample. As this study progressed, it raised questions about specific details of the experimental task and about the generalizability of the findings to other populations. I thus undertook a second study, this time in older people drawn from the community. One of the aims was to test whether the relationships (or lack of thereof) between ECDM performance and brain health measures observed in HIV generalized to older people without HIV. The ECDM task used in Chapter 3 has advantages over other ECDM tasks: it is simple to explain and administer and does not include additional considerations of risk or uncertainty. However, most of the studies in the literature that reported significant relationships between apathy measures and laboratory task performance in clinical samples used effort tasks where effort was more salient or used the Effort Expenditures for Rewards Task (EEfRT) which requires some effort on every trial and includes considerations of risk. To address whether the observed lack of a relationship between ECDM performance and motivation in Chapter 3 might have a technical basis, here we only included physical effort (handgrip) and adjusted the task to heighten the salience of effort, added the EEfRT task to assess convergent validity, and studied community-dwelling older people. I also took the opportunity to explore a second form of motivation: i.e intrinsic

motivation. This has received little attention in the clinical literature; although, it is known that intrinsic motivation generally has a large positive impact on performance in healthy people. The aim of the study reported in Chapter 4 was to contribute evidence for convergent validity of the EEfRT and an improved version of the handgrip ECDM task in community-dwelling older adults. A secondary aim of this study was to provide preliminary evidence of the contribution of a novel task probing intrinsic motivation in predicting self-reported motivation.

Comparison of Effort-Cost Decision-Making Tasks and Their Relation to Self-Reported Motivation in Community-Dwelling Older People

Gloria Castaneda[1], Nancy E. Mayo[2], Lisa Koski[3], and Lesley K Fellows[1].

[1]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University.

[2]Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Canada.

[3]Department of Neurology and Neurosurgery, McGill University.

Abstract

Motivation (or lack thereof, as seen in apathy) is an important determinant of health-related quality of life in older people. Currently there is no gold-standard measure of this complex construct, whether in cognitive neuroscience research or clinical contexts. Effort-cost decision making (ECDM) tasks have been developed to study the neural basis of motivation. These computerized tasks assess how hard a person is willing to work for a given monetary reward, and have been proposed as potential indicators of motivation. However, existing evidence for a relationship between ECDM performance and self-reported motivation is conflicting and focused on schizophrenia and Parkinson's Disease. This study aims to contribute evidence for a relationship between performance on the two most commonly used ECDM tasks, the Effort Expenditures for Rewards Task (EEfRT) and a handgrip effort-reward decision task, and self-reported motivation in a sample of 73 community-dwelling older adults. We also explored a second facet of motivation, so-called intrinsic motivation, using a novel task. We found no reliable relationship between the two ECDM tasks, and neither task was associated with self-reported motivation. There were individual differences in performance of the novel intrinsic motivation task, weakly related to self-reported motivation. While ECDM has face validity as an indicator of motivation, these findings suggest that a broader approach is needed to identify the facets of motivation relevant to real-world behavior in older people, and to optimize both self-report and task-based assessments of these facets.

Keywords: reward, effort, apathy, motivation, aging, neuroeconomics, human.

Introduction

Motivation is important for the well-being and quality of life of community-dwelling older adults. Apathy-a clinical syndrome characterized by lack of motivation-is linked to frailty, depression, cognitive decline and dementia in older adults (Bock et al., 2020; Groeneweg-Koolhoven et al., 2017; Johansson et al., 2020; Montoya-Murillo, Ibarretxe-Bilbao, Peña, & Ojeda, 2019; Semprini et al., 2012). Despite the adverse health associations, we lack robust methods to assess motivation, and (relatedly) the neural underpinnings of this capacity are poorly understood. Behavioral economics research offers novel frameworks for defining component processes of the multi-faceted construct of motivation, along with candidate laboratory tasks to assess these processes. This could add to our understanding of the brain basis of motivation, offering neurobiologically-informed models to improve diagnosis and treatment. The subjective cost of effort, as assessed in effort-cost decision making (ECDM) tasks, is the best-studied candidate component process of motivation, to date.

The most widely-used ECDM task is the Effort Expenditures for Rewards Task (EEfRT) (Treadway et al., 2009), in which participants choose between a low or high physical effort (rapid button presses) for varying amounts of money. The reward available is probabilistic, requiring consideration of risk as well as effort and reward. A second, simpler ECDM task has been used in several recent studies. This task asks participants to trade off monetary rewards and physical effort of different intensities exerted on a dynamometer (handgrip).

A recent review of ECDM studies in depression and schizophrenia showed that while some studies found an association between mental health symptom severity and a reduced willingness to exert effort for rewards, others found the opposite effect, i.e. symptom severity

was linked to increased willingness to exert effort, and others had null results. The authors of this review proposed that the inconsistencies might be explained by different neural mechanisms underlying variation in ECDM in depression and schizophrenia (Culbreth et al., 2018). Table 4.1 shows an extension of this literature summary, adding studies in any clinical sample and healthy individuals. This table summarizes studies published in English that included a self-report or interview measure of a brain health construct in addition to any type of ECDM task published between 2010 and June 2021. Health constructs included apathy, anhedonia, depression, fatigue or general health. Exclusion criteria included studies that used social rewards or studies that were already summarized in Culbreth et al., 2018. The bibliographic search included the terms “effort”, “reward” and “task” and was conducted in PubMed. To facilitate comparisons across studies, when not provided, we derived the correlation coefficient of the associations following published formulas (Cohen, 2013).

Table 4.1

Summary of studies relating effort-cost decision-making tasks to clinical brain health measures

Study	Construct	Sample	n	Task	Group effect?	Measure	Measure and task association?*	Cognitive measure	Cognitive measure and task association?
Bonnelle, Manohar, et al. (2015)	Apathy	Healthy	37	Handgrip	N/A	LARS-AI	r=.57 effort	NO	N/A
Bonnelle, Veroman K.R, et al.(2015)			50	Handgrip	N/A	LARS-AI	r=.36 effort	NO	N/A
Le Bouc et al. (2016)		PD	24 PD 25 HC	Handgrip	PD<HC	AES	r=-.47 reward	NO	N/A
Le Heron et al. (2018)			21 PD apathy 18 PD no-apathy	Handgrip	PD<HC	LARS	r=.37 acceptance	NO	N/A
Xinhua Yang et al. (2021)	Anhedonia	MDD;BD; SZ	37 MDD 32 BD depression 33 BD mania 30 Acute SZ 33 Stable SZ 43 HC	EEfRT	X X BD mania<HC Acute SZ<HC Stable SZ<HC	SHAPS TEPS-CON (only for BD mania)	r= .02 r= .06 r= .12 r= .41 r= .43 r= .20 acceptance	NO	N/A
Subramaniapillai et al. (2019)	Anhedonia; Depression	MDD	21 MDD 20 HC	EEfRT	X X	SHAPS; MADRS	r=.15 r=-.13 acceptance	THINC-it	r=.53
Lacourt et al. (2018)	Fatigue	Cancer	17 Cancer 30 Survivors	EEfRT	N/A	MFSI-SI	r=-.26 cancer ***r=.28 survivors acceptance***	NO	N/A
Draper et al. (2018)		LPS-induced	14 LPS 15 Placebo	Handgrip	LPS<Placebo	POMS	r=-.31 acceptance	NO	N/A
W. Chang, A. Chu, et al.(2019)	Negative symptoms; Anhedonia	FEP	45 FEP 45 HC	EEfRT	FEP<HC[a]	SHAPS SANS amotivation score	r=.16 r=-.23 [a,c] acceptance	NO	N/A
Bergé et al.(2018)	Negative symptoms	SZ	43 SZ 35 HC	Button press	SZ<HC	BNSS amotivation score	r=-.34 acceptance	NO	N/A
Cooper et al.(2019)			153 SZ 105 HC	EEfRT	SZ<HC	CAINS amotivation score	r(46)=.30[b] effort	MCCB	r(45)=-.02[b] effort
W. Chang, A. Westbrook, al.(2020)			40 FEP 44 HC	COGED	FEP<HC	BNSS amotivation score	r=-.23[c] reward	Digit symbol	r=.14
Kurniawan et al.(2010)	Propensity to work	Healthy	27	Grip task	N/A	Persis-tence scale	r=.59 acceptance	NO	N/A
Lasselin et al.(2017)	Sleep	LPS-induced	23	EEfRT	LPS>HC	KSS	***r=.46[a] acceptance***	NO	N/A

Note: PD, Parkinson's disease; HC, healthy control; FEP, first episode psychosis; MDD, major depressive disorder; LPS, lipopolysaccharide; SZ, schizophrenia; EEfRT, effort expenditure for rewards task; COGED, cognitive effort discounting task; LARS-AI, Lille apathy rating scale-Action initiation; AES, Apathy Evaluation Scale; LARS, Lille apathy rating scale; SHAPS, Snaith-Hamilton pleasure scale; TEPS-CON, Temporal Experience of Pleasure Scale- Consummatory Subscale; MADRS, Montgomery–Asberg depression rating scale; MFSI-

SI, Multidimensional Fatigue Symptom Inventory-Short Form; POMS, profile of moods state questionnaire; BNSS, brief negative symptom scale; SANS, scale for the assessment of negative symptoms; CAINS, clinical assessment interview for negative symptoms; KSS, Karolinska Sleepiness Scale; THINC-it, THINC-Integrated Tool; MCCB, MATRICS Consensus Cognitive Battery.

X= No group effect; N/A= Not applicable; NO= Not reported or explored in the study.

*Results for the association between brain health constructs including cognition and task performance are presented as correlation coefficients in all studies. The task outcomes were percentage of accepted offers or effort or reward sensitivity based on computational modelling of choices; when the second approach was used, it is specified if the association was found with the effort or reward sensitivity parameter. Bold italics correlation coefficients indicate instances where worse symptoms were linked to greater acceptance of effort.

[a] Association found only for the highest EEfRT probability level (i.e. 88%).

[b] Analysis done in Sample 2 (N=94 schizophrenia; N=66 HC).

[c] Results of correlation analysis.

As seen in Table 4.1, most of the studies used either the EEfRT or the handgrip task, or variations thereof. One study also assessed mental effort. Most of the studies reported the expected group differences (i.e. less willingness to exert effort for a given level of reward in patient groups compared to healthy controls), although three reported no group differences or the opposite pattern (Lasselin et al., 2017; Subramaniapillai et al., 2019; Yang et al., 2021). Nine studies found associations with individual differences in effort avoidance and worse symptoms (i.e. more apathy, less motivation, or less propensity to work) (Bergé et al., 2018; Bonnelle, Manohar, et al., 2015; Bonnelle, Veromann, et al., 2015; W. C. Chang et al., 2020; Wing Chung Chang et al., 2019; Cooper et al., 2019; Kurniawan et al., 2010; Le Bouc et al., 2016; Le Heron, Manohar, et al., 2018), two found the opposite effect (i.e. fatigue and reduced sleep) (Lacourt et al., 2018; Lasselin et al., 2017), while three reported null results (i.e. anhedonia, depression and fatigue) (Wing Chung Chang et al., 2019; Draper et al., 2018; Subramaniapillai et al., 2019).

Apathy and amotivation were the constructs most often related to ECDM task performance, while anhedonia, depression and fatigue were not associated with task performance in most studies. The differences in the extant literature may be due to neurobiological differences across samples and conditions. One study found that higher anhedonic symptoms in schizophrenia but not in depressive disorders was linked to effort avoidance in the EEfRT (Yang et al., 2021). Nevertheless, it is also possible that the inconsistencies are due to differences in the psychometric properties of the tasks. There is only one study comparing the psychometric properties of different ECDM tasks in schizophrenia, finding medium associations between tasks (Horan et al., 2015; Reddy et al., 2015). In that two-part study, a binary choice handgrip task showed weak external validity in schizophrenia whereas the EEfRT showed good external

validity. Both tasks discriminated between healthy controls and patients and had good test-retest reliability.

Another potential explanation for the lack of consistent relationships between ECDM performance and real-world motivation is that ECDM is not a component process that is consistently relevant to real-world motivated behavior. Motivation is a complex construct that includes behavior driven by intrinsic considerations such as curiosity, novelty seeking, or the inherent satisfaction of the action itself, as well as by the potential for an external reward (Ryan & Deci, 1985). Indeed, intrinsic motivation may even be reduced by external rewards (Murayama, Matsumoto, Izuma, & Matsumoto, 2010). While intrinsic motivation has been little studied in the context of motivational disorders, it is known to have a large positive impact on academic, athletic, and occupational performance in healthy people (Cerasoli, Nicklin, & Ford, 2014). There has been some work on the neural substrates of intrinsic motivation, albeit with small sample sizes and varied tasks, suggesting that areas known to be important to reward processing, such as the striatum, are recruited during intrinsically motivated behaviors (Lee & Reeve, 2017; Murayama et al., 2010).

The main aim of the present study is to contribute evidence for convergent validity of the EEfRT and a Handgrip Effort Task as laboratory measures related to self-reported real-world motivation in community-dwelling older adults. A secondary aim is to explore the association between performance of a novel task probing intrinsic motivation and self-reported motivation.

Methods

Participants

A sample of seventy-four participants (age range: 55-83) was recruited from the McGill Cognitive Neuroscience Research Registry which in turn draws from the general public through social media advertisements and community centers in Montreal, Canada. Inclusion criteria for this study were age 55 years or older and able to communicate in French or English sufficient to provide written informed consent and understand task instructions. Exclusion criteria included history of a neurological disorder likely to affect cognition, recent consumption of medication or drugs that might affect thinking like anti-depressants, tranquilizers, or drug or alcohol addiction, or a Montreal Cognitive Assessment (MoCA) score < 24. Eighty-two people were recruited. Six performed below the pre-defined cut-off on the MoCA (Nasreddine et al., 2005), leaving 74 participants to continue in the study.

This study was approved by the Research Ethics Board of the McGill University Health Center. All study participants received monetary compensation of CAD$30 for their participation plus the earnings from each of the tasks in this study.

Self-Report Measures

Motivation

Motivation was measured using the Starkstein Apathy Scale-Rasch (SAS-R). This is a version of the Starkstein Apathy Scale (SAS) (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992) optimized via Rasch analysis (Smith, 2004) using this methodology (Hum et al., 2021). Based on the results from this analysis item 3 “Are you unconcerned about your condition” was removed as it did not fit the construct of motivation in this sample of healthy

participants. Logit scores from the final 13 items were transformed to a 0-26 scale for easier comparison with the other measures. Motivation is measured on a continuum with higher scores indicating more motivation.

Cognitive Symptoms

The Communicating Cognitive Concerns Questionnaire (C3Q) is an 18-item self-report questionnaire initially developed for specific cognitive concerns relevant to people with HIV and subsequently shown to be appropriate to identify cognitive concerns in a large Canadian community sample (Askari et al., 2020). The C3Q assesses memory, attention, executive function, and language. The total score ranges from 0 to 36, with higher values indicating better cognition (i.e. fewer cognitive symptoms).

Depression and Anxiety

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) was used to assess anxiety and depression symptoms. The HADS is a 14-item scale: 7 items assess anxiety (HADS-A), and 7 items assess depression (HADS-D). The linear hierarchy and validity of the items have been tested (Pallant & Tennant, 2007). To facilitate the comparison between the HADS and the other brain health measures of this study, the original scale was reversed so that higher scores indicated better mood (i.e. fewer symptoms).

Vitality

The RAND-36 measure of health-related quality of life Energy/Fatigue subscale (Hays & Morales 2001) was used to assess vitality (lack of fatigue). The nine items of this subscale are answered along a 5-point ordinal scale, ranging from “All the time” to “None of the time”. As

for the other brain health measures, the scores were reversed so that higher scores indicate more vitality.

Performance Measures

Cognitive Performance

The Brief Cognitive Ability Measure (B-CAM) (M. J. Brouillette et al., 2015) is a cognitive performance test that includes a series of tasks assessing episodic memory (word list recall), working memory (Corsi block test), and executive functions (Flanker task, Trail-Making Task-B, phonemic verbal fluency). This assessment provides a global measure of cognitive ability with a total score ranging from 0-41, with higher scores indicating better cognitive performance.

Effort-Expenditure for Rewards Task

A comparison of the ECDM tasks is presented in Table 4.2. The EEfRT requires participants to choose between a “hard task” (i.e. 100 button presses) for a “high reward” (i.e. range between $1.25-$4.30), and an “easy task” (i.e. 30 button presses) for a “low reward” (i.e. $1.00). After selection of the task, participants have 21s to complete the hard task and 7s to complete an easy task. There are three levels of probability of being a win trial, 12%, 50% and 88% probability. At the end of each trial participants receive feedback on whether they successfully completed the effort and whether they won the reward at stake. Participants played for 15 minutes and at the end of the game are paid for their performance in two of their win trials, selected at random. For more details on the task and experimental procedure please refer to Treadway, Bossaller, Shelton, & Zald (2012). The duration of the task was modified following Barch, Treadway, & Schoen (2014). This task was presented using Psychophysics Toolbox implemented for MATLAB (MathWorks, USA).

Handgrip Task

After completion of the EEfRT, participants completed the Handgrip task, implemented in Cogent 2000 (www.vislab.ucl.ac.uk) for MATLAB (MathWorks, USA). This was a modified version of the task used in Study 2 in (Bonnelle, Veromann, et al., 2015). Participants' maximum voluntary contraction (MVC) was calculated before the task by asking them to squeeze a hand dynamometer with their dominant hand as hard as they could, twice. The average of these two values was considered their 100% MVC. Once this value was calculated, participants completed a *"Force-level familiarization"* block where they were asked to generate all effort levels used in the handgrip task , using their dominant hand, for 2s, starting at level one (i.e. 20% MVC) up to level five (i.e. 100% MVC). The *Force-level familiarization* was followed by a "*Practice block"* of 5 trials that simulated the real task.

The task included four "*Decision blocks"* with 35 combinations each, corresponding to the six different reward levels (i.e. 0,1, 3, 6, 9, and 12 apples), and six effort levels (i.e. 0%, 20%, 40%, 60%, 80% and 100% MVC). The 0 apple and 0% effort choice was not presented. Participants indicated their choice on each trial but were not required to produce the selected effort. After each "*Decision block*" a random trial was drawn from the previous 35 responses and was played "for real". If they had accepted that offer, participants had 5s to reach the required force level and hold it for 2s with their dominant hand to win the apples at stake. If they had rejected that offer, then they had to wait for 5s for the next decision block to began and received no apples. At the end of the task, the apples collected were converted to cash compensation, with $6.24 dollars the maximum possible.

Table 4.2

A descriptive comparison of ECDM tasks

Task Condition	Handgrip Task	Effort Expenditure for Rewards Task (EEfRT)
Description	Participants make decisions (i.e. Accept/Reject) in every trial.	Participants chose between two options (i.e. low effort & low reward vs high effort & high reward).
Response Type	Self-paced.	5s to make a decision and 7s or 21s to execute effort.
Effort and Reward levels	6 effort levels, 6 reward levels.	2 effort and 2 reward levels.
Execution of effort	Effort is calibrated relative to individual ability and exerted using a hand dynamometer[a].	Effort is not calibrated and is exerted using button presses.
Probability of reward	100%	3 levels (12%, 50% and 88%)
Number of Trials	140 trials with 5 practice trials	20 minutes[b] to complete a maximum of 120 trials with 3 practice trials.
Outcome measure	Proportion of accepted offers across all reward and effort levels.	Proportion of selection of hard choices for each probability level (i.e. 12%, 50%, and 88%).

Note: [a] Frequency of effort execution across the task varies across studies (e.g., once at the end of each block or every time an offer is accepted).

[b]Duration of the EEfRT may vary between studies.

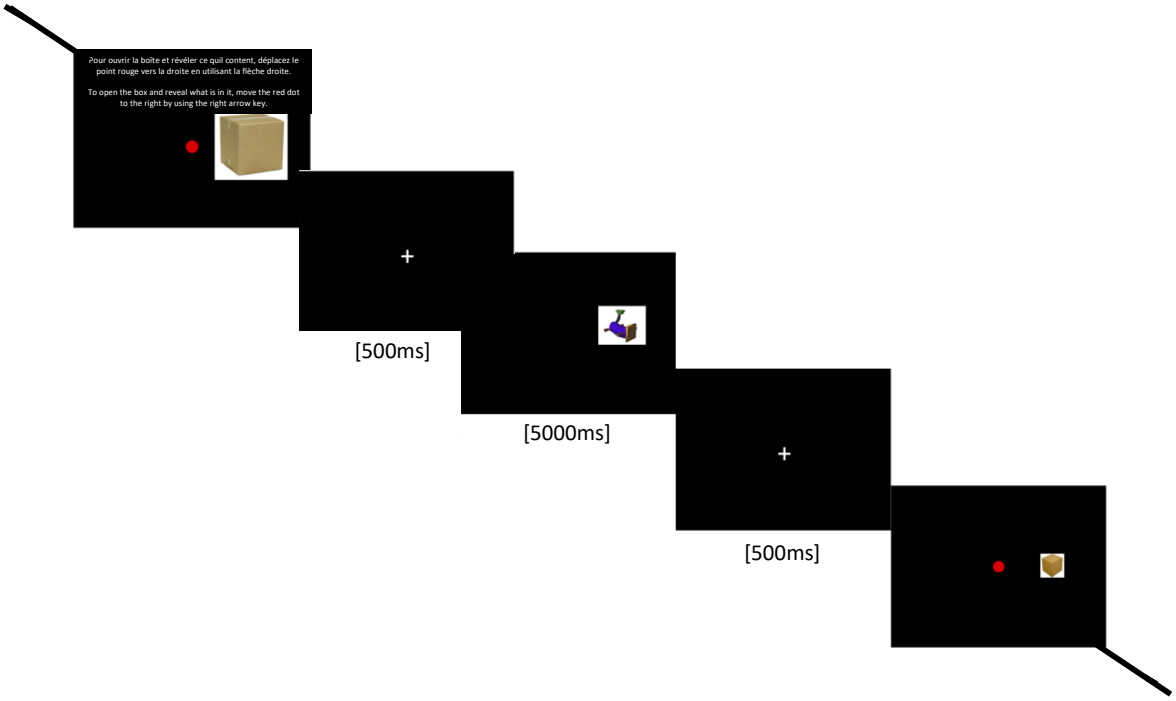
Intrinsic Motivation Task

After finishing both ECDM tasks, participants were informed of their total earnings. If sufficient time remained in the planned 120 min testing session, participants were then invited to complete the intrinsic motivation task. Fifty-three participants were invited for this task.

The Intrinsic Motivation Task was inspired by the Stop Watch Task, which has been used previously to study intrinsic motivation (Murayama et al., 2010; Takeda et al., 2017). Here, we used novel visual images (fribbles (Barry, Griffith, De Rossi, & Hermans, 2014)) instead of the points system used in the Stop Watch Task, and the effort requirement (button presses) increased on each trial. The tester excused herself on the pretext that she had to photocopy the payment receipt, and participants were left alone in the testing room for 6 minutes while they waited for her to return. They were given the option to "try out a new task" or read some magazines while they waited, if they wished. The "new task" was cued up on the computer screen, which showed instructions in French and English explaining how to initiate the task: "To open the box and reveal what is in it, move the red dot to the right by using the right arrow key". Each time the right arrow key was pressed, the red dot moves to the right one pixel. Once the red dot reached the box, an image of a novel complex object (fribble) was shown for 5000 ms, followed by a fixation cross of 500 ms and then a new trial. On subsequent trials, the box was smaller, thus more keypresses were required to move to open it. Initial trial required 13 keypresses, increasing to 30 keypresses by the final trial. The entire task took 5 to 6 minutes to complete; participants could stop responding at any time. The dependent measures were initiation of the task (yes/no) and if yes, the total number of trials completed.

Figure 4.1

Illustration of the Intrinsic Motivation task



Note: Participants start the task by pressing the right arrow key on their keyboard to start moving the red dot towards the box to open it. After the red dot reaches the box (15 key presses for the first trial), participants are presented with a fixation cross for 500 ms, followed by presentation of a novel visual image for 5000 ms, and a second fixation cross for 500 ms. The box is progressively smaller on each subsequent trial, so that ~ 1 additional key press is needed to open it.

Statistical Analysis

To characterize the sample, we calculated the mean [*M*] and standard deviation [*SD*] of the demographic and brain health measures of all participants. Since several participants were unable or unwilling to complete the EEfRT task, we performed a logistic regression to evaluate

whether there were differences in the demographic or brain health measures between the group that completed only the Handgrip task and the group that completed both the Handgrip and EEfRT tasks.

To contribute evidence for convergent validity of the EEfRT and the Handgrip task as measures of motivation, each participant's proportion of accepted offers was calculated for each task. We calculated four ECDM outcome measures: Proportion of hard choices for the EEfRT for each reward probability (12%, 50%, 88%) and proportion of accepted offers across all trials for the Handgrip task. Correlation analysis was used to test the relationship between ECDM task performance and self-reported motivation. Finally, we conducted a third set of correlations between the task outcome measures and other brain health measures (i.e. depression, cognition, etc). This last step evaluated the specificity of the hypothesized relationship between task outcome measures and self-reported motivation.

Sample size calculations were conducted a priori for each aim. We anticipated a high correlation between effort tasks; 29 participants would be needed to detect large effects. For the association between effort tasks and brain health measures, a sample size of 85 would detect a medium effect with 80% power at an alpha level of 0.05. Sample size calculations were done using G*Power (Faul, Erdfelder, Lang, & Buchner, 2007).

The exploratory aim of this study was addressed with regression to test whether initiating the IMT (yes/no) or number of trials completed was associated with greater self-reported motivation.

Results

A sample size of 100 was targeted a priori, but only 82 people could be successfully recruited within the timeframe of the study. Of those, eight did not fit the inclusion criteria. Seventy-four participants completed the brain health measures and the handgrip task (MoCA M= 27.76, SD= 1.76). Technical problems meant that usable data were not available for one participant, so the final dataset included 73 participants. Demographic and brain health characteristics of the sample are presented in Table 4.3. All 73 participants completed the handgrip task. Only 49 of these also completed the EEfRT. Participants who refused or were not physically able to do the EEfRT had a history of arthritis, reported that the button presses were uncomfortable, or had poor dexterity that prevented them from completing the task in the allotted time. As seen in Table 4.3, there were no differences in demographic or brain health measures between those who completed both tasks and those who only completed the handgrip task (95% CI included the null value of 1.0)

Table 4.3

Demographic and brain health characteristics of the sample by number of tasks completed

Characteristics and Measures	Handgrip Task (full sample) N=73		Handgrip Task and EEfRT N=49		Only Handgrip Task N=24		Handgrip Task and EEfRT vs Only Handgrip Task	
	M	*SD*	*M*	*SD*	*M*	*SD*	*OR*	95% *CI LL, UL*
Personal characteristics								
Age (Years)	64	7.14	64	6.60	65	8.23	0.97	0.91, 1.04
Women/Men	26/47		17/32		9/15		1.21	0.43, 3.36
Education (Years)	16	2.57	16	2.63	16	2.51	1.03	0.84, 1.25
Self-reported Brain Health Constructs								
SAS-R (Motivation) [0-26][a]	20.58	3.25	20.41	3.40	20.96	3.02	0.96	0.82, 1.12
C3Q (Cognitive symptoms) [0-36]	29.76	6.08	29.06	6.19	30.95	5.79	0.95	0.86, 1.05
HADS-D (Depression) [0-21][b]	18.38	2.72	18.27	2.81	18.50	2.59	0.94	0.77, 1.14
HADS-A (Anxiety) [0-21][b]	15.85	2.78	15.65	3.02	16.29	2.20	0.92	0.76, 1.11
RAND-36 (Vitality) [0-100]	73.95	12.78	73.15	12.74	75.65	12.97	0.98	0.94, 1.02
Performance measure								
B-CAM (Cognitive performance) [0-35]	19.13	3.18	19.27	3.33	18.85	2.93	1.03	0.87, 1.21

Note: C3Q, Communicating Cognitive Concerns Questionnaire; HADS, Hospital Anxiety and Depressive Scale; B-CAM, Brief Cognitive Ability Measure; M, mean; SD, standard deviation

[a] Higher scores indicate more motivation.

[b] Scores were reversed so that higher scores indicate fewer symptoms.

Table 4.4 shows task performance measures and the associations between them for the two ECDM tasks, for the group that completed both (N=49). Given the distribution of

the data, non-parametric correlations were used. In the EEfRT, participants played an average of 27 (SD 16.2) trials. Of those, 72% (SD 23) were successfully completed (i.e. participants produced the required effort). The mean choice reaction time (RT) was 1.42 (SD 0.54) seconds for all trials; M=1.44 (SD= 0.6) for the 12% reward probability trials; M=1.38 (SD= 0.6) for 50% reward probability trials and, M=1.46 (SD=0.62) for 88% reward probability trials. Mean percentage of acceptance of hard task choices across all probability levels was 31.77 (SD= 24.00). There was a significant effect of effort ($F(5,360)= 111.1$, $p<.001$), and reward ($F(5,360)= 225.6$, $p<.001$) on selecting a hard choice. There was also a significant interaction of effort and reward ($F(24,1728)= 20.53$, $p<.001$) on hard task choices. No effects of age or sex were observed. As seen in Table 4.4, acceptance rates for the hard choice in the 12%, 50%, and 88% reward probability trials were correlated with each other (Spearman rho>.7).

Table 4.4 also shows handgrip task performance. Mean RT was 1.49 (SD=0.54) seconds. There was a significant effect of effort on the proportion of accepted trials ($F(5,360)= 111.1$, $p<.001$), an effect of reward amount ($F(5,360)= 225.6$, $p<.001$) and a significant interaction of effort and reward ($F(24,1728)= 20.53$, $p<.001$). No effects of age or sex were found. There was no significant correlation between proportion of hard choice selection in the EEfRT at any of the reward probability levels and proportion of accepted offers in the Handgrip task .

Table 4.4

Correlation (Pearson r) [95% confidence intervals] of ECDM performance (percentage of accepted offers) within and across tasks, for the group that completed both tasks (N=49)

Task/condition	*M*	*SD*	*1 .*	*2.*	*3.*
1. EEfRT 12%	26.95	24.93	-		
2. EEfRT 50%	29.90	23.81	**.89** [0.84,0.93]	-	
3. EEfRT 88%	38.67	30.03	**.73** [0.58,0.89]	**.69** [0.49,0.90]	-
4. Handgrip Task	59.90	15.92	.18 [-0.12,0.48]	.23 [-0.08,0.54]	.03 [-0.28, 0.34]

Note: Bolded correlation coefficients are significant associations p<0.05.

A second, *post-hoc* analysis was undertaken to relate the present findings to the existing study that compared performance on different ECDM tasks in the same sample. This followed the methods described in Reddy et al., (2015). Effort levels of the Handgrip task were collapsed into "low" (≤ 40%), and "high" (≥ 60%). Reward levels were collapsed into three: "low" (≤1), medium (≥3), and "high" (≤6). A reward difference score was also calculated for each effort task (proportion of acceptance of hard choices during the highest reward level – proportion of acceptance of hard choices during the lowest reward level). A probability difference score was calculated for the EEfRT task (proportion of acceptance of hard choices during the highest probability level – proportion of acceptance of hard choices during the lowest probability level). We found no significant correlation between the two tasks difference scores (reward difference, r_s= -0.226, p=.091 ; probability difference,

r_s=-.108, p>.4). The mean reward difference score of the handgrip task M=23.36% (SD=9.87) was larger than the EEfRT M=12.07% (SD=18.32) (i.e. greater difference scores indicate more willingness to exert effort for large rewards compared to small rewards).

Table 4.5 shows the correlation between brain health measures and EEfRT performance for all three probability levels. There were low to moderate correlations for all of the brain health measures with at least one of the EEfRT conditions except for the SAS-R, a measure of self-reported motivation.

Table 4.5

Correlation (Spearman rho) [95% confidence intervals] of brain health measures and proportion of accepted offers in the EEfRT, by reward probability condition

Brain Health measures	Handgrip Task and EEfRT *N=49*		
	12% probability	50% probability	88% probability
Self-reported			
1. SAS-R[a]	-.118 [-0.387,0.170]	-.080 [-0.354,0.206]	.096 [-0.195, 0.387]
2. C3Q	.209 [-0.095, 0.513]	.257 [-0.026, 0.541]	**.286** [-0.003, 0.575]
3. HADS-D[b]	.044 [-0.270, 0.358]	.003 [-0.313, 0.318]	.226 [-0.089, 0.539]
4. HADS-A[b]	**.306** [0.032, 0.578]	**.298** [0.015, 0.579]	**.348** [0.092, 0.602]
5. RAND-36	.257 [-0.045, 0.558]	.229 [-0.088, 0.546]	**.306** [0.005, 0.606]
Performance			
6. B-CAM	.227 [-0.071, 0.524]	.140 [-0.140, 0.419]	**.305** [0.034, 0.575]

Note: Bolded correlation coefficients are significant associations p<0.05.

SAS-R, Starkstein Apathy Scale-Rasch; C3Q, Communicating Cognitive Concerns Questionnaire; HADS-D, Hospital Anxiety and Depressive Scale-Depression Score; HADS-A, Hospital Anxiety and Depressive Scale-Anxiety Score; B-CAM, Brief Cognitive Ability Measure.

[a] Higher scores indicate more motivation.

[b] Scores were reversed so that higher scores indicate fewer symptoms.

Table 4.6 shows the same relationships for the Handgrip task for all 73 participants who completed that task, the sub-group that completed both tasks (N=49), and participants who only completed the Handgrip task (N=24). The correlation between self-reported motivation

(SAS-R) and other brain health measures and proportion of accepted offers was near zero, except for self-reported cognitive symptoms, where a moderate correlation was observed: range 0.3 to 0.42, although confidence intervals were wide, and the lower bound of the 95% CI was near zero for two groups and included zero for the group that only completed the Handgrip task.

The same logistic regression shown in Table 4.3 was performed for the percentage of accepted offers in the Handgrip task, comparing the group that completed one task to the group that completed both tasks. The group that completed both tasks (M=59.90; SD=15.92) had slightly higher odds of having a higher percentage of accepted offers in the Handgrip task than the group that completed only the Handgrip task (M=49.97; SD=12.06) OR=1.06, 95% CI= 1.01, 1.10.

Table 4.6

Correlation (Spearman rho) [95% confidence intervals] of brain health measures and proportion of accepted offers in the Handgrip task, by groups defined in Table 4.3

Brain Health measures	Handgrip Task (full sample) N=73	Handgrip Task and EEfRT N=49	Only Handgrip Task N=24
Self-reported			
1. SAS-R[a]	-.096 [-0.320, 0.138]	-.096 [-0.328, 0.136]	-.017 [-0.418, 0.389]
2. C3Q	**.301** [0.071, 0.501]	**.360** [0.126, 0.592]	**.417** [-0.002, 0.711]
3. HADS-D[b]	.012 [-.219, 0.241]	.009 [-0.308, 0.326]	-.058 [-0.451,0.354]
4. HADS-A[b]	.124 [-0.110, 0.345]	.214 [-0.098, 0.526]	-.163 [-0.533, 0.260]
5. RAND-36	-.004 [-0.235,0.228]	.018 [-0.307, 0.344]	-.010 [-0.420, 0.404]
Performance measure			
6. B-CAM	.102 [-0.133, 0.327]	.002 [-0.334, 0.338]	.293 [-0.134, 0.628]

Note: Bolded correlation coefficients are significant associations p<0.05.

SAS-R, Starkstein Apathy Scale-Rasch; C3Q, Communicating Cognitive Concerns Questionnaire; HADS-D, Hospital Anxiety and Depressive Scale-Depression Score; HADS-A, Hospital Anxiety and Depressive Scale-Anxiety Score; B-CAM, Brief Cognitive Ability Measure.

[a] Higher scores indicate more motivation.

[b] Scores were reversed so that higher scores indicate fewer symptoms.

Table 4.7 presents the characteristics of the participants who had the opportunity to engage with the intrinsic motivation task, and their performance on that task. Due to time constraints, only 53 participants had the opportunity to try this task (33 men, mean age= 63.00, SD= 7.55; 20 women, mean age= 64.30, SD= 6.79). Of these, 13 participants (mean age= 65.31, SD=5.45) did not engage with the task (8 men) and 40 (mean age=55, SD=7.69) initiated the task (25

men). The mean number of trials completed for those who initiated the task was 6.54 (SD= 6.18), range 1-1/30 trials. Participants who initiated the task were younger (M=62.98, SD= 6.67) than those who did not (M= 65.15, SD=8.78) but this difference was not significant, t(51)-.945, p=.349, 95%CI=-6.809, 2.452. Those who initiated the task also had numerically higher SAS-R scores (i.e. more motivation) (M=20.65, SD=2.81) than those who did not (M=19.31, SD=3.40). An exploratory logistic regression analysis revealed that self-reported motivation was not significantly associated with initiating the IMT, OR=1.181, 95% CI=0.945, 1.476. High motivation did not reliably predict the number of trials completed, although a trend in this direction was observed B=0.495, 95% CI= -0.076, 1.067.

Table 4.7

Demographic information and self-reported motivation measure of the sample that was offered the Intrinsic Motivation Task (IMT), by number of IMT trials completed (N=53)

Number of trials completed						
	0	<1*	4	8	12	16
N	13	3	8	8	11	10
Motivation						
SAS-R [a]	21.8 (3.2)	21.6 (2.1)	21.0 (2.7)	22.0 (3.2)	20.7 (2.9)	21.6 (2.4)

Note: [a] Higher scores indicate more motivation.

Mean (SD). * Participants initiated the task but did not complete the first trial.

Discussion

Apathy has been recognized as a risk factor for mortality, cognitive decline, delirium, dementia, and frailty in older people (Hölttä et al., 2012; Semprini et al., 2012; Willem van Dalen et al., 2018), but little work has been done to define the mechanisms underlying low motivation in this population. This study tested the validity of two laboratory tests of effort-reward trade-off: the EEfRT and a handgrip ECDM task, as candidate indicators of self-reported motivation in community-dwelling older adults. Preliminary evidence was also gathered for a novel task probing intrinsic motivation. Tasks assessing the component processes of motivation could be useful for identifying the causes of and testing potential interventions for low motivation in older people. Such tasks could also advance research on the brain mechanisms of low motivation, offering a neurobiological rationale for assessment and treatment.

While effort-cost decision making, i.e. the willingness to work harder for a given monetary reward, has face validity as a factor in motivation, there is relatively weak evidence for existing laboratory tasks in this regard. Here, we report the convergent validity of the EEfRT and a Handgrip ECDM task, in a sample of community-dwelling older adults.

All participants in this study were able to complete the Handgrip task. However, a substantial minority had difficulty carrying out the standard EEfRT, largely due to limitations of manual dexterity or physical discomfort with the many button presses required. Thus, a first conclusion is that further application of the EEfRT in elderly samples will require modification of the task. Amongst those who completed both ECDM tasks, the expected effects of effort and reward on choice were present, suggesting that they understood both tasks. However, there was no correlation between performance on these tasks. This is in contrast with one published

study that found a moderate correlation between the difference scores of the EEfRT, and the difference scores of a binary choice Handgrip task (with only two effort levels) in a sample with schizophrenia (Horan et al., 2015; Reddy et al., 2015). Of note, there are substantial methodological differences between that handgrip task and the one used here. Following a similar procedure, we found no significant associations between difference scores of both tasks. Although a trend was observed, convergence validity could not be claim with such a low correlation coefficient, even if the association were to be significant. Moreover, those analysis resulted in many inflexible responders (i.e. responders that accepted or rejected all options in the highest effort level) as a result of combining the effort levels.

Overall, in our study, there was a higher acceptance of hard choices in the Handgrip task compared to the EEfRT, likely because effort in the standard EEfRT was more salient (each trial was played) and not calibrated for individual capacity, reducing acceptance of hard choices. In addition, the reduced selection of hard choices observed in the EEfRT may be explained by temporal discounting (i.e. hard EEfRT choices required more time to complete, as more button presses were needed), or risk avoidance associated with age; neither construct is relevant to the Handgrip task.

The lack of association between ECDM task performance and self-reported motivation observed here may be because correlations between self-report and performance measures tend to be weak, given the inherent differences in these two forms of assessment (Dang et al., 2020; Goodwin et al., 2016). Small samples and publication bias for positive findings may explain the pattern in the existing literature. In addition, we note that the published studies reporting an association between apathy and ECDM performance mainly

used a clinician rating scale (Lille Apathy Rating Scale; (Sockeel et al., 2006)) rather than self-report measures of motivation, as used here. The former focuses more on everyday function (actions), while the latter asks mainly about self-beliefs regarding level of motivation (i.e. 'I need a push to get started…'). In recent work in older people with chronic HIV infection, we found that ECDM performance was related more to actions (i.e. hours spent in goal-directed activities) than to the beliefs about motivation assessed with the SAS-R (Castaneda et al., 2021) The present findings are consistent with the idea that laboratory measures of ECDM may have more promise as indicators of real-world observable motivated activities than to self-ratings of motivation. These distinctions have not always been clear in the existing literature, but we suggest they are important in moving towards a robust research framework on motivation and apathy in older people and in clinical populations.

ECDM is only one of several candidate component processes relevant to motivated behavior in older people. Other elements of decision-making, such as option generation, reward anticipation, action initiation, and interaction with the goal may also be important (Barch et al., 2019; Fellows, 2004; Husain & Roiser, 2018). Similarly, there are other facets of motivation that have yet to be explored. Here we took a preliminary step towards a broader approach, assessing intrinsic motivation with a novel task. This task shows preliminary evidence for a relation between voluntary engagement in a task (specifically completing more trials) and self-reported motivation.

Finally, we asked whether performance in these tasks associated with other facets of brain health. Those with fewer cognitive symptoms had higher acceptance rates in both tasks. Higher acceptance on the EEfRT (88% probability) was also linked to less anxiety, more vitality (less

fatigue) and better cognitive performance. The findings suggest that the EEfRT may be more suitable than the Handgrip task for future work in this vein but could be simplified by including only the 88% reward condition and would need to be adapted for the physical restrictions common even in the healthy elderly.

To our knowledge, this is the second study to assess validity of two ECDM. This study also included a comprehensive assessment of multiple brain health constructs. These measures were distributed across the range of possible scores suggesting that the measures were able to detect variability (except for mood and cognition, which were positively skewed in this community sample). Participants reported a range of motivation, although scores were slightly higher compared to previous work in clinical samples (Castaneda et al., 2021).

An important limitation is that there was missing data for two tasks due to technical or physical constraints which resulted in a sample size too small to detect small associations.

There were no ceiling or floor effects in the prespecified dependent measures for either task. Overall percentage of acceptance was slightly lower compared to other EEfRT studies in PD and schizophrenia (Wing Chung Chang et al., 2019; Le Heron, Manohar, et al., 2018; Reddy et al., 2015), but percentage of acceptance was similar to existing studies testing the same handgrip task on healthy young individuals (Bonnelle, Manohar, et al., 2015; Draper et al., 2018).

The present findings could help explain some of the mixed results in the ECDM literature. The EEfRT shows potential to be used in older adults but risk and temporal discounting should be accounted for when interpreting the results. Future tasks using versions of this handgrip task should focus on making effort more salient. Finally, neither of the ECDM tasks was related to

self-report motivation. This finding, in the context of our own work in another sample, and the existing literature, suggests that ECDM tasks may be better related to demonstrated real-world motivated behavior than to subjective beliefs about motivation as assessed by self-reported apathy scales.

Notes

Authors have no conflicts of interests to declare. We thank Masud Husain, Alexander Soutschek, Philippe Tobler and Todd Hare for sharing versions of the ECDM task and for their input during the design phase of this study. We also thank Stanley Hum for his help with the analysis. This work was supported by a grant from the Velux Foundation with support from the Brain@McGill programme and the Healthy Brains for Healthy Lives CFREF grant to McGill University.

Chapter 5

Reward-Related Evoked Potentials as Markers of Low Motivation in Older People Living with HIV.

Preface

The two previous chapters examined whether performance on ECDM tasks was related to real-world motivation. These studies provided evidence that self-reported real-world activity is related to performance measures of motivation. These two studies used an ECDM task, which draws on one of the proposed key components of goal-directed behavior i.e. subjective cost of effort. However, as outlined in the introductory chapter of this dissertation, other component processes of goal-directed behavior might also be relevant to low motivation. A limited number of studies have focused on these other aspects of goal-directed behavior in the context of motivation; for this next chapter I will focus on another stage of goal-directed behavior: the interaction with the goal. This stage includes the hedonic response that can have a positive or negative impact, which is a more well-defined and studied process, compared to effort processing.

We used high-density EEG and a task in which choices were made and gain or loss feedback was delivered to contribute evidence of the extent of the relationship between two electrophysiological correlates of feedback processing and indicators of real-world motivation in a sample of participants with well-controlled HIV. This new sample was drawn from the same cohort as the study reported in Chapter 3. This last study examined whether two EEG correlates of feedback processing could serve as potential neural markers of motivation.

Reward-Related Evoked Potentials as Markers of Low Motivation in Older People Living with HIV.

Gloria Castaneda[1], Ana-Lucia Fernandez Cruz[1], Marie-Josée Brouillette[2], Nancy E. Mayo[3], and Lesley K Fellows[1].

[1]Department of Neurology and Neurosurgery, Montreal Neurological Institute, McGill University.

[2]Department of Psychiatry, Faculty of Medicine, McGill University

[3]Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Canada.

Abstract

Apathy, a clinical disorder characterized by low motivation, is prevalent in people living with Human Immunodeficiency Virus (HIV). It affects mental and physical health-related quality-of-life, medication adherence, and is associated with cognitive decline. However, the causes of low motivation in HIV and the underlying brain mechanisms are unknown. Brain responses to reward may be relevant to understanding the mechanisms of low motivation and might serve as biomarkers for diagnosis or testing interventions. Electroencephalogram (EEG) responses to gain and loss feedback in simple guessing tasks have been related to apathy in neurodegenerative conditions and in healthy individuals. The primary aim of this study is to contribute evidence on the extent of the relationship between two EEG correlates of reward processing, the Reward Positivity, and the Feedback-P300, and real-world motivation indicated by self-reported hours spent on meaningful activities per week, in older individuals with well-controlled HIV infection. High-density EEG was collected from 75 people living with HIV while they performed a guessing task with gain or loss feedback. We found that the later component of reward processing, the feedback-P300, was related to engagement in meaningful activity, while the earlier Reward Positivity was not. This study investigated two EEG markers of motivation in people living with HIV; the findings lay the groundwork for a better understanding of the neurobiology of low motivation in this condition.

Keywords: HIV/AIDS, electroencephalogram,, motivation, feedback, biomarkers.

Introduction

Apathy is prevalent in psychiatric and other chronic health conditions, including neurodegenerative disorders. Since the introduction of combination antiretroviral therapy (cART), Human Immunodeficiency Virus (HIV) infection is considered a chronic condition (van Sighem, Gras, Reiss, Brinkman, & de Wolf, 2010). As people live longer with HIV, they face multiple complications and challenges to their mental and neurological health (Heaton et al., 2010; Kamat et al., 2016; Kaur et al., 2019). Apathy, a multifaceted syndrome characterized by reduced motivation, is frequent in people living with HIV, even with cART (McIntosh et al., 2015). This syndrome is associated with dependence in activities of daily living, medication nonadherence, and poor mental and physical health-related quality of life (Barclay et al., 2007; Kamat et al., 2016, 2012). Currently, the diagnosis of apathy relies on self-report ratings or clinician interviews. A biomarker could shed light on the mechanisms underlying this syndrome and facilitate diagnosis and testing of treatments.

Neuroscience research has proposed conceptual frameworks that dissect apathy into more specific component processes, including responses to reward (Barch et al., 2019; Fellows, 2004; Husain & Roiser, 2018). Electroencephalogram (EEG) techniques are a suitable method to study reward-related processes in the brain (Glazer et al., 2018). Given the relatively low cost and wide accessibility compared to other imaging methods, EEG is a method that might be readily translated to clinical settings; this may be especially relevant for the care of people in resource-poor settings where HIV is endemic.

The Reward Positivity (RewP), is a reward-specific event-related potential (ERP). This ERP has a positive deflection observed at frontocentral electrodes at around 200 to 300 ms that

differentiates monetary gains and losses, or gain and loss feedback, during outcome processing (Proudfit, 2015). The feedback-P300 (FB-P3) is a P300 ERP elicited by feedback and sensitive to outcome details, including reward magnitude (Glazer et al., 2018; Sato et al., 2005). The FB-P3 appears as a positive-going deflection at centroparietal electrodes immediately following the RewP (300 ms - 600 ms) (Proudfit, 2015). Similar to the RewP, the FB-P3 distinguishes gain and loss feedback (San Martín, 2012).

Two studies have tested the relationship of the RewP with apathy symptoms. One reported null findings in healthy individuals (Takayoshi, Onoda, & Yamaguchi, 2018), and another reported a significant association between the amplitude of the RewP and self-reported apathy in Parkinson's Disease (PD) (Martinez-Horta et al., 2014). However, both studies involved small samples and mainly focused on the RewP difference (i.e. the difference between loss and gain, or ΔRewP). Studies of people with depression have shown an association between symptoms of depression and the ΔRewP (Belden et al., 2016; Brown, Richardson, & Cavanagh, 2020). There is also preliminary evidence that the FB-P3 could be a marker for apathy, in a sample of 14 healthy young adults (Takayoshi et al., 2018).

There are different approaches for assessing clinical apathy. In research settings, self-report is more feasible than clinician ratings. The Starkstein Apathy Scale (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992) is the self-report measure of apathy most widely used in research. However, a recent study showed that this scale has psychometric limitations at the item level (Hum, Fellows, Lourenco, & Mayo, 2021). In addition, none of the available self-report measures of apathy has been validated for HIV. Information on real-world engagement is an alternative indicator of apathy. Previous studies in HIV have shown that

apathy was related to real-world behaviors, such as a decline in activities of daily living (Kamat et al., 2012) and fewer self-reported hours spent on meaningful activities per week (Mayo et al., 2020). Meaningful activity has been linked to greater emotional and physical well-being as well as motivation in older adults (Hooker, Masters, Vagnini, & Rush, 2020a; Mayo et al., 2020). In a previous study in HIV, we also demonstrated that time spent on meaningful activities was related to a laboratory performance measure of motivation (Castaneda et al., 2021).

Here, we contribute evidence regarding the relationship between the amplitudes of two EEG potentials elicited by feedback in a guessing task, the RewP and FB-P3, and two indicators of real-world motivation: time spent on meaningful activities and items from a self-reported apathy scale, in older people with HIV. We hypothesized that the conditional waveform for gain feedback for both the RewP and the FB-P3 will be positively associated with hours spent on meaningful activity, thus serving as potential neural biomarkers for motivation. All hypotheses and analyses were pre-registered (https://osf.io/yemhn).

Material and Methods

Participants

Eighty-five people with well-controlled HIV participated in this study. Data were collected as part of a baseline assessment for two pilot randomized trials of interventions to improve cognition (physical exercise or computerized cognitive training). These were sub-studies sampling from the Positive Brain Health Now (BHN) cohort (Mayo et al., 2016). The BHN cohort is a longitudinal study of brain health in older individuals living with HIV in Canada.

Resting and task-evoked high-density EEG was collected to test potential biomarkers of brain health constructs including cognition and motivation. Data from the routine BHN visit closest in time to the EEG session (self-report questionnaires on brain health and function, cognitive performance) were also included. Inclusion criteria in the main BHN cohort were age 35 years or older, HIV infection for at least one year, and ability to communicate in French or English. Exclusion criteria included clinically diagnosed dementia severe enough to preclude informed consent, life expectancy of fewer than 3 years, other non-HIV-related neurological disorders likely to affect cognition, current substance use disorder or severe substance use disorder within the past 12 months, and active CNS opportunistic infection or hepatitis C on interferon treatment, or presence of psychotic disorder. Participants in the cognitive training trial also required access to the Internet, while those in the physical exercise trial reported sedentary behavior (i.e., moderate physical activity for no more than 30 minutes and no more than twice a week) and were excluded if they had cardiovascular or musculoskeletal contraindications for vigorous exercise. Three participants were excluded from the current analysis due to poor quality EEG data. The protocol was approved by the Research Ethics Board of the McGill University Health Centre and all study participants provided written informed consent.

Real-world Motivation

Participants reported the number of hours they spent in a typical week doing self-directed activities that are considered to be personally meaningful such as reading, checking email, surfing the internet, crafts or hobbies, or other leisure activities. Questions were derived from the Community Healthy Activities Model Program for Seniors (CHAMPS) (Stewart et al., 2001). Meaningful activity was used as the primary indicator of motivation, given previous results from our research group suggesting it is a more promising indicator of real-world motivation in HIV for the purposes of linking with neurobehavioral constructs than clinical questionnaires, (Castaneda et al., 2021).

Nonetheless, to allow the present work to be related to the wider literature, participants also completed the Starkstein Apathy Scale- Rasch version (SAS-R) (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992). Eight items were administered from the 14-items of the standard Starkstein Apathy Scale (SAS) and re-scored to provide a semi-quantitative measure of motivation, based on a Rasch analysis performed on this data. Scores were transformed from logit scores to a 0 to 100 scale, where higher values indicate higher motivation.

Electrophysiological Measures

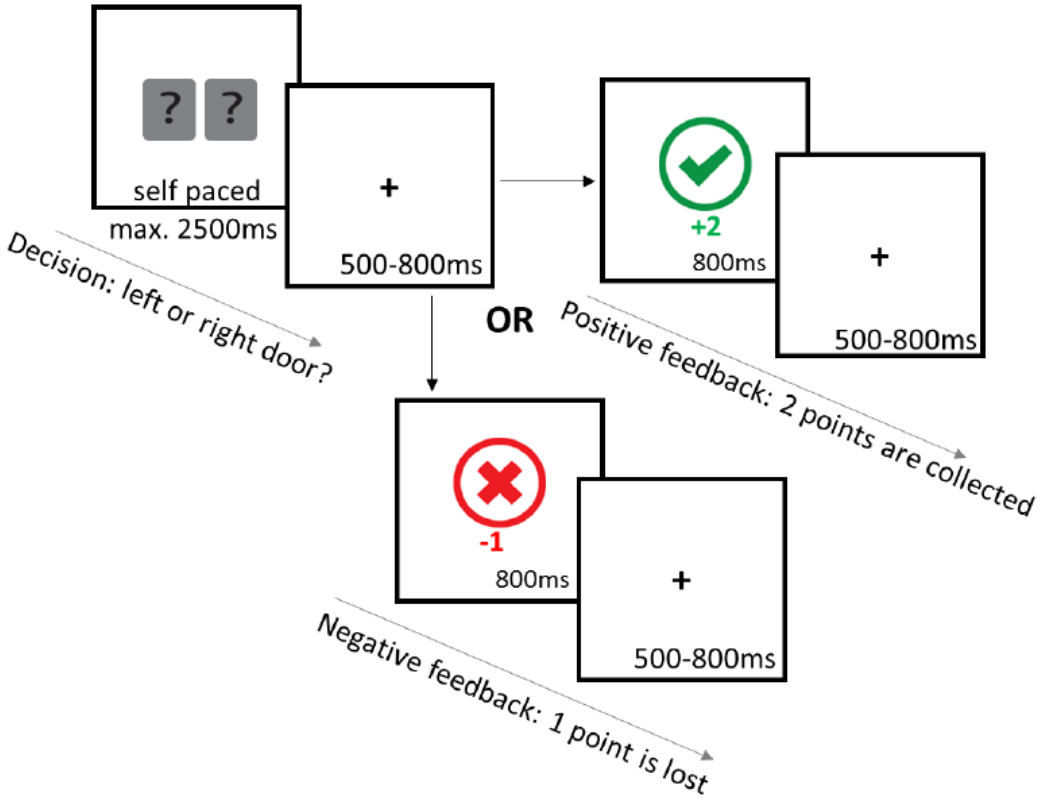
Guessing task.

This task was a modified version of the Doors task (Gehring, 2002; Martinez-Horta et al., 2014), with 150 trials divided into 5 blocks. As illustrated in Figure 5.1. a trial began with the presentation of the stimuli for 2500ms. i.e., two doors on either side of the screen. The participant selected a door with the “right arrow” or the “left arrow” key, using their index

fingers. A fixation cross was then presented in the center of the screen followed by feedback presentation for 800ms. Gain feedback was worth two points, signaled by a green checkmark, whereas loss feedback was the loss of one point, signaled by a red 'x'. The next trial began with the presentation of a fixation cross with a duration randomly selected from the following times: 550ms, 650ms, 750ms, 850ms, 950ms, or 1590ms. All trials had a 50% probability of gain or loss feedback, regardless of the choice made. This probability was unknown to participants, who were instructed to "try your luck to choose the winning door from the two doors" and were encouraged to collect as many points as possible. Point totals were presented every 30 trials to keep participants engaged and motivate them to collect more points.

Figure 5.1

Schematic showing the guessing task.



Electroencephalographic Data Acquisition and Analysis

A 256-channel high impedance HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR) with NetStation 5 acquisition software from the same company was used to record the electrophysiological data of participants while they completed the task. Electrodes were mounted in an elastic cap and electrode impedance was kept below 50 kΩ. Data were collected with a sampling rate of 1000 Hz using the electrode Cz as a reference, with online visualization filters of 60Hz for Notch, 5Hz for high-pass, and 120 Hz for low-pass. The seventy-eight

electrodes located on the neck and cheeks were routinely contaminated with muscle artefact and were removed in all participants before data pre-processing.

EEG data were processed offline for all subjects using Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011), a freely available software available under the GNU general public license (http://neuroimage.usc.edu/brainstorm). EEG recordings were filtered using a bandpass filter of 0.1-30 Hz, down-sampled to 500 Hz, and re-referenced to the right and left mastoid electrodes. Bad channels were manually identified with power spectrum density plots using Welch's method and manual examination of the raw signal. Segments that showed oscillating signals higher than 200 μV were discarded. If the entire channel signal was consistently above this threshold, then that channel was removed. Automatic blink detection was conducted on the four electrodes located above and below each eye with a frequency band between 1.5 to 15Hz, a threshold of 2 standard deviations, with the minimum duration between two events set to 800ms. Blink detection was additionally manually verified. Signal-Space Projection was used to detect other artifacts including blinks and non-blink events; only components that capture at least 20% of the artifact's signal with frontal spatial distribution were selected.

The time window of interest for the EEG analysis was 800ms after feedback onset (gain and loss). A baseline correction of -200 ms before feedback onset was applied. Epochs with an activity of ± 100 μV were rejected. Electrophysiological trials corresponding to behavioral trials with missing responses or responses with a reaction time of less than 5 milliseconds were removed. The average number of electrophysiological trials included for gain and loss feedback was comparable (N=74 (SD=6.10), and N=74 (SD=6.21), respectively).

ERP Analysis

The RewP was measured between 200-300 ms following feedback onset. This time window was selected based on previous publications (Glazer et al., 2018; Peterburs, Suchan, & Bellebaum, 2013). The RewP has a frontocentral distribution; for this study, we analyzed the RewP at a cluster of electrodes centered at FCz (i.e. E015, E006, E023 in the 256-channel EEG system (Luu & Ferree, 2005)) where it typically peaks (Holroyd & Krigolson, 2007; Miltner, Braun, & Coles, 1997), and a cluster centered at Fz (E021, E013, E028), a site used in previous studies using lower-density EEG systems (Hajcak, Holroyd, Moser, & Simons, 2005) including the only study to date showing a link to self-reported apathy: Martinez-Horta et al (2014) reported RewP amplitude differences between PD patients with and without apathy. The cluster approach was taken here to make the most of the high-density EEG data.

The FB-P3 was measured at centroparietal electrodes 300-600 ms after feedback presentation. This time window was selected following previous studies (Glazer et al., 2018; Peterburs et al., 2013). The analysis of the FB-P3 was conducted on the mean amplitude of the signal in the selected time window for a cluster of electrodes centered at Cz (E081, E045, E132) and Pz (E101, E129, E100) (Hajcak et al., 2005; S.C. Kleih, Nijboer, Halder, & Kübler, 2010; Peterburs et al., 2013; Polich, 2007) where this ERP typically peaks.

The N1 is an ERP reflecting early sensory processing (Luck, Woodman, & Vogel, 2000) that here served as a check on the specificity of the hypothesized relationships. This ERP was assessed at a cluster centered at Cz where the distribution is typically maximal (E081, E045, E132) 90-120 ms after feedback presentation. This selection of electrodes is consistent with previous studies (Debruille, Touzel, Segal, Snidal, & Renoult, 2019).

Statistical Analyses

The main effects of feedback condition on the RewP and FB-P3 were tested using a repeated-measures ANOVA with two factors: condition (gain, loss) and clusters. Multiple linear regression was conducted to assess the contribution of each ERP (i.e., RewP mean amplitude of the gain feedback condition, and FB-P3 mean amplitude of the gain feedback condition) on predicting the primary real-world outcome, i.e. hours of meaningful activities per week. Given the ample evidence that age influences EEG signal, age was included in the models (Gajewski, Ferdinand, Kray, & Falkenstein, 2018; Rossini, Rossi, Babiloni, & Polich, 2007). We performed the same regression model for the secondary motivation measure (i.e., SAS-R) to facilitate comparisons with the existing literature.

Additional exploratory analysis examined the signal from single electrodes (i.e., FCz= E015, Fz= E021, Pz= E101, Cz= E081) to test whether the effects observed at clusters were also present at the single electrodes used more frequently in the literature (mostly studies using 64-channel EEG). We also explored the contribution of the ΔRewP (i.e., loss minus gain feedback condition), and the mean amplitudes of the loss feedback condition per ERP (RewP and FB-P3) on predicting each of the two outcome measures of real-world motivation. Lastly, to explore the contribution of HIV infection severity to the brain changes reflected in the ERPs, we conducted a regression analysis testing the effect of nadir CD4 on RewP and FB-P3, with age included in the models.

Results

Participant Characteristics

Demographic information, HIV-related clinical characteristics, and real-world motivation measures are presented in Table 5.1. From all 75 participants with EEG data suitable for analysis 92% were taking antiretrovirals at the moment of the study.

Table 5.1

Demographic and clinical characteristics of the sample (N=75).

Characteristics	*M or %*	*SD*	*Median*
Age (Years)	54.84	6.99	53.80
Men	89%		
Women	11%		
Education (Years)	12.97	3.30	12.00
Duration of HIV infection (Years)	17.81	7.22	18.00
Current CD4 cell count (cells/µL)	649.17	256.04	640.00
IQR	481-836		
0-199	4.33%		
200-500	21.33%		
> 500	73.33%		
Nadir CD4 cell count (cells/µL)	213.62	157.33	170.50
IQR	133-256		
Plasma Viral Load			
Virologically suppressed (≤50 copies/mL).	93.33%		
Self-reported measures			
Meaningful activity [h/week]	33.22	23.07	31.00
SAS-R (Motivation) [0-100]	52.04	13.83	49.98
HADS-D (Depression) [0-21][a]	15.84	4.01	17.00
HADS-A (Anxiety) [0-21][a]	13.99	4.38	14.00
Performance measure			
B-CAM (Cognitive performance) [0-35]	20.42	4.23	20.50

Note. In all self-reported measures higher scores indicate more motivation. IQR= Interquartile range. SAS-R= Starkstein Apathy Scale-Rasch; HADS, Hospital Anxiety and Depressive Scale; B-CAM, Brief Cognitive Ability Measure.

[a] Scores were reversed so that higher scores indicate fewer symptoms.

Feedback-Related Evoked Potentials

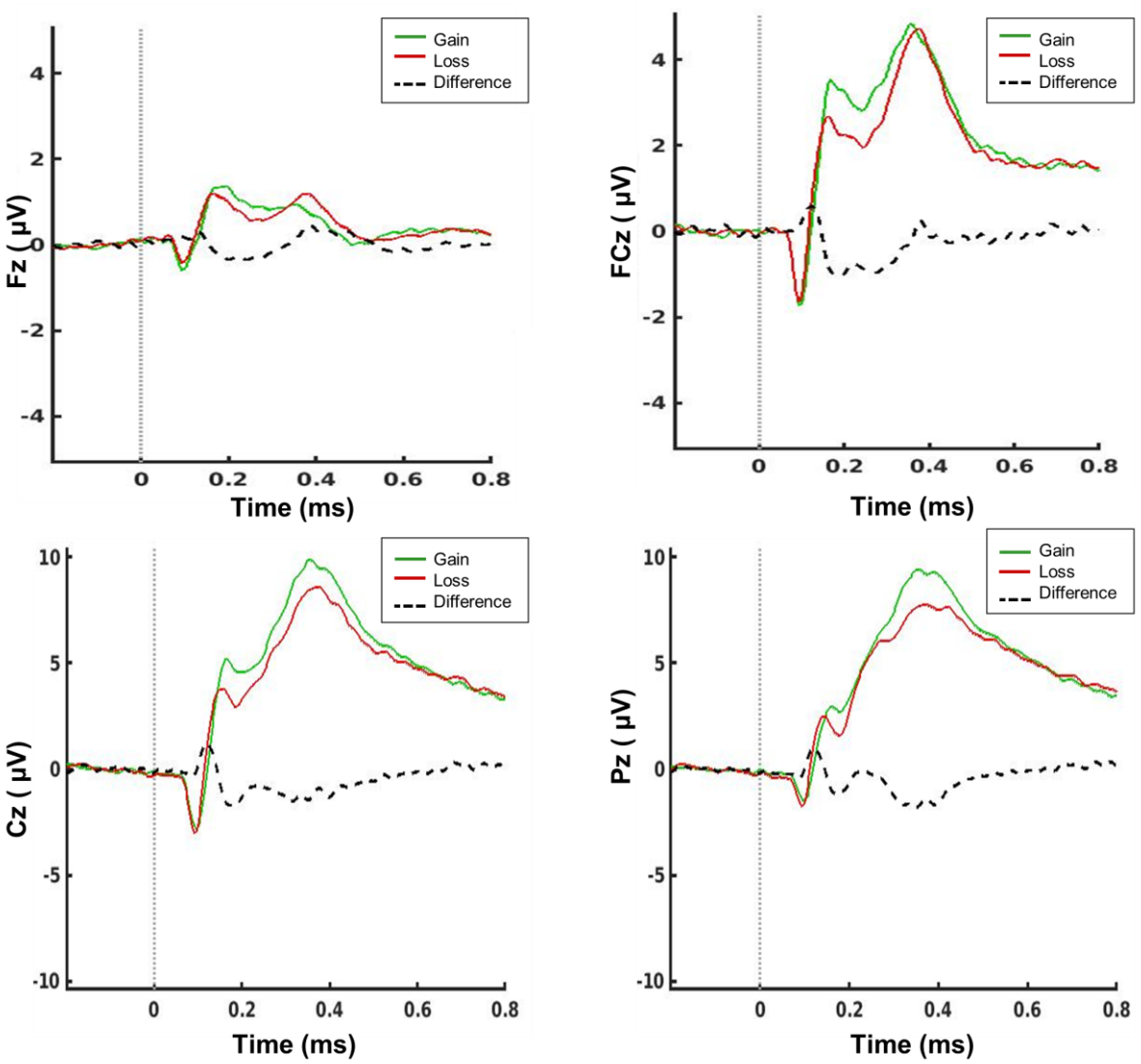
Participants completed an average of 99.84% (SD=0.01) of trials out of the 150 available. There was a significant effect of feedback condition $F(1,74)= 65.14$, $p< .001$, $\eta^2=0.47$ and cluster site $F(1,74)= 25.87$, $p< .001$, $\eta^2=0.26$ and a significant interaction $F(1,74)= 26.96$, $p< .001$, $\eta^2=0.27$ on the mean amplitude of the RewP. Post-hoc comparisons (Bonferroni-corrected) revealed that the mean amplitude of the RewP was significantly larger for gain feedback than for loss feedback ($p<.001$), as expected, and that the mean amplitude at cluster site FCz was significantly larger than the mean amplitude at cluster site Fz ($p<.001$), as seen in Figure 5.2.

There was also a significant effect of feedback condition $F(1,74)= 7.18$, $p= .009$, $\eta^2=0.09$ on the mean amplitude of the FB-P3. There was no effect of cluster site, nor interaction. Post-hoc pairwise comparisons (Bonferroni-corrected) revealed that the mean amplitude of the FB-P3 was significantly greater for gain than for loss feedback ($p=.03$). There was also a significant effect of feedback type on the N1 $F(1,73)= 13.68$, $p<.001$, $\eta^2=0.16$, with the amplitude significantly larger for gain feedback than for loss feedback ($p<.001$).

Figure 5.2 shows the grand averages of all the evoked potentials elicited by gain feedback, loss feedback, and the difference of loss minus gain feedback, during the guessing task at cluster sites.

Figure 5.2

Evoked Related Potentials in response to feedback



Note: ERPs for gain feedback (in green), loss feedback (in red) conditions, and the mean difference of loss minus gain feedback (black dotted line). The RewP (200-300 ms after feedback presentation) was measured at a frontocentral cluster. The FB-P3 (300-600 ms after feedback) was measured at a centroparietal cluster.

Relationships Between Gain Feedback-Evoked Potentials and Real-World Motivation

Multiple linear regression models were fitted to evaluate if EEG potentials evoked after gain feedback condition were related to the planned primary indicator of real-world motivation (time spent on meaningful activities in a typical week). As seen in Table 5.2, there was a significant relationship between hours of meaningful activity and the amplitude of the FB-P3 at both clusters: Cz ($F(2, 71) = 3.74$, $p = .029$) and Pz ($F(2, 71) = 5.47$, $p=.006$), with no effect of age at either cluster site ($p> .1$). That is, for every increase of 1 μV in the amplitude of the FB-P3 gain conditional average at Pz there was an increase of 2 hours of meaningful activity per week. In contrast, there was no significant relationship between the RewP gain conditional average at Fz ($p>.5$) or FCz ($p = .06$) and time spent on meaningful activities (Figure 5.3). Meaningful activity was also not predicted by the N1 amplitude ($p>0.5$). Exploratory analysis of the ERPs amplitudes at single electrodes confirmed the results from the cluster analysis, i.e. only the amplitude of the FB-P3 at Pz was significantly related to meaningful activity ($p=.009$), with no effects of age ($p>.6$); ($F(2,71) =4.11$, $p=.020$).

Table 5.2

Multiple linear regressions predicting time spent on meaningful activities

Outcome: Meaningful activities (h/wk), 33.22 (23.07) **Predictors**	**Parameter Estimate (*b*)**	**Standard Error**	**95 % CI (lower bound, upper bound)**	**R^2**
	Gain feedback			
RewP amplitude, µV	2.15	1.12	(-0.08, 4.38)	
Age, decades	-2.83	3.82	(-10.44, 4.78)	0.06
FB-P3 amplitude, µV	2.06**	0.76	(0.55, 3.57)	
Age, decades	-1.64	3.78	(-9.17, 5.89)	0.11*
N1 amplitude, µV	-0.86	1.20	(-3.25, 1.53)	
Age, decades	-4.47	3.98	(-12.41, 3.47)	0.02

Note: Results are from clusters centered at FCz for RewP and at Pz for FB-P3 gain feedback conditional averages. To facilitate interpretation, age is expressed in decades. $^{*}p < 0.05$; $^{**}p < 0.01$; ***p < 0.001.

In a planned secondary analysis, multiple linear regression models were also run to test the relationship between RewP (p>.2), FB-P3 (p>.3), and N1 (p>.6) gain feedback conditional averages and self-reported motivation (SAS-R). No significant relationships were found for any of the cluster sites (Supplementary Table 5.1).

Relationships Between EEG Potentials Evoked by Loss Feedback and Feedback Difference and Real-World Motivation

As seen in Table 5.3, time spent on meaningful activity was also predicted by the amplitude of the FB-P3 loss conditional average at both clusters Cz (F (2,71)=3.76, p=0.28) and Pz (F (2,71) =3.62, p=.032), with no effect of age. An increase of 1 µv in the amplitude of the FB-P3 loss conditional average at Pz predicted 1.92 more hours of meaningful activity per week. Meaningful activity was not significantly predicted by the RewP loss conditional average or the

ΔRewP. None of the ERPs were related to the secondary measure of motivation (SAS-R) (supplementary Table 5.2).

Table 5.3

Multiple linear regressions predicting real-world motivation (meaningful activities)

Outcome: Meaningful activities, 33.22 (23.07) **Predictors**	**Parameter Estimate (*β*)**	**Standard Error**	**95 % CI (lower bound, upper bound)**	**R^2**
Loss feedback				
RewP amplitude, μV	2.16	1.11	(-0.05, 4.38)	
Age, decades	-3.43	3.79	(-10.98, 4.13)	0.06
FB-P3 amplitude, μV	1.92**	0.77	(0.39, 3.46)	
Age, decades	-2.30	3.77	(-9.82, 5.22)	0.09*
N1 amplitude, μV	0.01	0.94	(-1.87, 1.89)	
Age, decades	-3.84	4.15	(-12.11, 4.32)	0.01
Difference (loss-gain)				
ΔRewP, μV	0.17	2.60	(-5.03, 5.36)	
Age, decades	-3.82	3.95	(-11.69, 4.06)	0.01

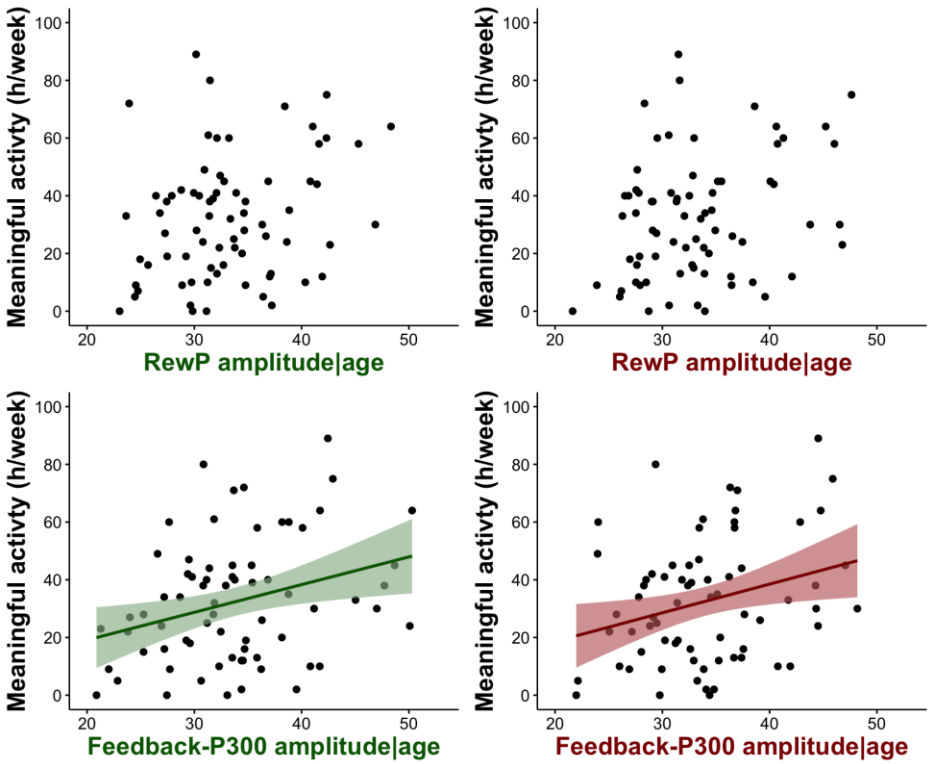
Note: Results are from a cluster centered at FCz for RewP and a cluster centered at Pz for FB-P3 loss feedback conditional averages. The ΔRewP is calculated as the difference between loss minus gain feedback. To facilitate interpretation, age is expressed in decades. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

Relationship Between Feedback-Evoked Potentials and HIV Severity

Finally, we tested if past HIV infection severity, a variable related to variation in brain structure measured with MRI in other studies, contributed to the observed variation in neural activity in response to feedback here. Neither of the two conditional waveforms (gain or loss feedback), or their difference for the RewP or FB-P3 were predicted by nadir CD4 cell count.

Figure 5.3

Relationship between the amplitude of feedback-evoked potentials and time spent on meaningful activities



Note: Top row shows scatterplots of the relation between RewP gain feedback condition (in green) or RewP loss feedback condition (in red) adjusted for the effects of age, and time spent on meaningful activity in a week. Bottom row shows the relation between FB-P3 gain feedback condition (in green) or FB-P3 loss feedback condition (in red) adjusted for the effects of age, and meaningful activity. Shading shows the 95% confidence intervals.

To explore whether the two measures of real-world motivation were related, we performed a Pearson correlation. Meaningful activity and SAS-R were not significantly correlated (r= 0.14, *p*= 0.25). In addition, to explore whether less engagement in real-world activity might reflect individual differences in other brain health constructs, we correlated

number of hours of meaningful activity with a performance test of global cognitive ability (measured with the Brief Cognitive Ability Measure; B-CAM (M. J. Brouillette et al., 2015)), and self-reported anxiety and depression (measured with the Hospital Anxiety and Depression Scale; HADS (Zigmond & Snaith, 1983)), which were available as part of the BHN dataset. Only cognitive ability was significantly related to meaningful activity (r= 0.28, *p*=0.02).

Discussion

Apathy is a common and function-limiting problem in people living with HIV, but the underlying mechanisms are unclear. Reduced motivation is a core feature of the apathy syndrome. Fundamental neuroscience research on reward and punishment processing may be relevant to understanding low motivation in clinical populations (Barch et al., 2019; Fellows, 2004; Husain & Roiser, 2018). Here, we asked whether EEG correlates of feedback processing elicited with a simple guessing task related to real-world motivation indicated by hours spent on meaningful activities per week and by self-reported motivation in middle-aged and older people living with well-treated HIV. This was the first EEG study to investigate the RewP and FB-P3 in HIV. In this study, we showed that the amplitude of the FB-P3 conditional waveforms following gain or loss feedback, but not the amplitude of the RewP, predicted time spent on meaningful self-directed activities, and that this relationship was not explained by age or nadir CD4 count.

Performance feedback provides information about the goal-relevance of actions taken and can be studied with EEG components that are sensitive to loss (i.e. information about incorrect performance) and gain feedback (i.e. information about correct performance) (Holroyd, Larsen, & Cohen, 2004). Here we hypothesized that responses related to gain

feedback would be most informative, reasoning that they might be relevant to the 'approach' behaviors driving real-world activity. However, our findings suggest that response to feedback in general is relevant to understanding individual differences in motivation in people with HIV. We found that hours spent on meaningful activities per week were predicted by the amplitude of the FB-P3 in response to both conditions gain and loss feedback. That is, a reduced FB-P3 response to feedback, regardless of valence, was associated with less time spent on meaningful activities. The findings from this study are in line with one previous study conducted on healthy young people that also found an association between apathy and reduced amplitude of the FB-P3, albeit in a much smaller sample (Takayoshi et al., 2018).

P300 responses are not unique to feedback. Indeed, they can be elicited by a variety of events. In general, this component is thought to be made up of two sub-components: P3a (with a frontocentral distribution), and P3b (with a temporoparietal distribution) (Conroy & Polich, 2007). The P300 elicited by feedback has been suggested to be a P3b wave due to its topographical distribution (Balconi & Crivelli, 2010; Takayoshi et al., 2018). Our study and the study of Takayosi et al. (2018) linked the P3b to motivated behavior. However, there is also evidence linking the P3a evoked by novel stimuli in oddball tasks to self-reported apathy in a variety of samples, including healthy participants (S.C. Kleih et al., 2010; Sonja C. Kleih & Kubler, 2013), PD (Mathis et al., 2014), and after stroke (Yamagata, Yamaguchi, & Kobayashi, 2004). Oddball tasks engage cognitive-attentional processes whereas the guessing task used here measures initial response to feedback. The decreased FB-P3 activity observed in less motivated participants here could be related to impairments in cognitive processes including memory storage, and the continuous updating of task-relevant feedback information (Palidis, Cashaback,

& Gribble, 2019; Polich, 2007). The observed association between cognitive performance and real-world engagement here is in line with that notion. Overall, these findings suggest that the P300 could be a useful electrophysiological indicator of apathy in HIV.

It is possible that distinct aspects of apathy are linked to specific P300 waves. It has been proposed that there are three apathy domains: reduced goal directed behavior, reduced goal directed cognition, and reduced concomitants of emotion (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992). The cognitive domain could be reflected by the oddball-P3a, reflecting attention and working memory, whereas both the behavioral and possibly the cognitive domains of apathy linked to feedback processing could be reflected by FB-P3b waves. Future work could pursue these distinctions, to provide a more mechanistically specific account.

We did not find any significant relationship between ΔRewP (i.e. difference waveform) and meaningful activities. This is in line with the one study conducted on healthy participants (Takayoshi et al., 2018) but in contrast with a study in PD, which found that reduced amplitude of the ΔRewP was linked to apathy symptoms (Martinez-Horta et al., 2014). Variations in apathy may have different underlying mechanisms in PD than in healthy individuals or individuals living with HIV. A typical method to assess the RewP is by subtracting the mean amplitude of one of the two feedback types from the other (ΔRewP). This subtraction method is not so commonly applied to P300 waves but is quite common in studies of the RewP component. The difference wave method was proposed for the RewP as this ERP was initially conceived of as an error-related negativity driven by loss feedback (Gehring, 2002; Miltner et al., 1997). However, more recent studies have argued that this ERP is rather a reward-sensitive ERP driven by gain

feedback (Holroyd, Krigolson, & Lee, 2011). Others have argued that this ERP is generated by the contribution of both loss and gain feedback together but that each feedback-related response is likely generated by separate neural substrates: the anterior cingulate cortex and basal ganglia, respectively. This may explain some of the inconsistences in the literature (Foti, Weinberg, Bernat, & Proudfit, 2015). We had initially hypothesized that the conditional waveform to gain feedback would be related to meaningful activity, based on studies in depression that found that links between the ΔRewP and depressive symptoms were driven by gain feedback rather than loss feedback (Belden et al., 2016; Brown et al., 2020). Here, the ΔRewP did not show any relationship with meaningful activity nor self-reported apathy and the conditional waveforms to gain and loss feedback only showed trend effects. The lack of significant effects observed for ΔRewP and the RewP conditional waveforms and apathy could be explained by the task. This guessing task was a simplified version compared to other versions that have been used in previous RewP studies (Gehring, 2002; Martinez-Horta et al., 2014; Takayoshi et al., 2018). Some of these versions included different probabilities of gains or loss. Similarly to our study, the probability of feedback was set to 50% in the study in healthy participants that had similar results to ours (i.e. apathy was related to FB-P3 but not RewP) (Takayoshi et al., 2018). Lastly, given the variety of time range measurements and electrodes used in all RewP studies, it is possible that the RewP signal reported in some previous studies may have overlapped with the FB-P3 reported here.

Self-reported apathy measured with items derived from the widely used SAS (S. . Starkstein et al., 1992) was not related to RewP or FB-P3 conditional waveforms or differences in this study. Currently, there is no validated scale to measure apathy in HIV. The SAS has been

widely used in the larger literature on apathy, in its original 14-item format, but this form has psychometric limitations (Hum et al., 2021). Here, we used a version with better measurement properties (Smith, 2004), yet found no relationship with the EEG measures.

This is the second study that uses a real-world indicator such as meaningful activity as an index of motivation in HIV. In a recent study from our group that also drew participants from the BHN cohort, we also found that individual differences in meaningful activities but not SAS-R were linked to a performance measure of motivated behavior, in that case a laboratory effort-cost decision-making paradigm (Castaneda et al., 2021). The number of hours spent on activities that are personally meaningful per week is a measure based on the CHAMPS, often used in clinical assessments in occupational therapy (San Francisco, CA: University of California, 2003). Participation and active engagement that are personally meaningful lead to improved emotional and physical well-being in older adults (Eakman, 2012; Eakman, Carlson, & Clark, 2010), and have been linked to more vitality (less fatigue) and fewer depressive symptoms in healthy adults (Hooker, Masters, Vagnini, & Rush, 2020b). Here, we used this clinical metric as an indicator of apathy, on the premise that motivation is necessary for pursuing these types of real-world activities. However, we acknowledge that engagement in real-world activity is a global indicator that could also reflect limitations in other capacities, including executive function, anxiety, or depression. In our data, more hours of meaningful activity were related to better cognitive performance.

In a recent study from our group conducted on a sample overlapping with the one reported here, variation of the P300 amplitude evoked during an oddball task was explained by past HIV severity indicated by nadir CD4 cell counts (Fernandez Cruz et al., 2021). Here,

variation of the FB-P3 was not explained by this indicator of past immunosuppression. These contrasting findings suggest that the P300 elicited by oddball tasks and the FB-P3 in this guessing task likely reflect activity in distinct neural circuits, differently susceptible to direct HIV-related injury. This is supported by the wider literature. The oddball-evoked P300 is thought to be a P3a response, linked to prefrontal, frontal, and anterior temporal regions, while the brain regions that have been suggested to generate the P3b (i.e. generated by feedback), are posterior temporal, parietal, and posterior cingulate (Conroy & Polich, 2007; Spyrou & Sanei, 2008). Direct effects of HIV at the time of initial or untreated infection may preferentially affect the fronto-striatal systems thought to underpin the oddball-evoked P3a (Plessis et al., 2014). The brain basis for the variation in the FB-P3 here linked to real-world engagement remains to be established. Candidates include co-morbidities common in HIV that also affect the brain, such as cerebrovascular injury (Brew, Crowe, Landay, Cysique, & Guillemin, 2009; Cysique & Brew, 2019; Lam, Mayo, Scott, Brouillette, & Fellows, 2019; Sanford, Fellows, et al., 2018)). This would be a fruitful direction for future work, as it might suggest specific lifestyle or other interventions relevant to improving motivation and real-world engagement in people with chronic HIV infection.

We also included the N1 in the present analyses, to test the specificity of the hypothesized relations between the two ERPs of interest in this study and real-world motivated behavior. This ERP is elicited by onset of visual stimuli and reflects very early sensory and attentional processes (Luck et al., 2000). There is some evidence that the N1 is generated by activity in the dorsal stream in the vicinity of V3 (Di Russo, 2003; Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002). While we observed an effect of feedback condition on N1 amplitude,

this activity was not related to real-world behavior or self-reported motivation. There were also no effects of nadir cd4 status or age. This suggests that the association between FB-P3 and real-world motivation is specific to later brain processes, i.e. is not driven by non-specific arousal or attentional effects.

This study has limitations. First, only 8 women participated, so the results should not be generalized to women until they are replicated in a larger sample. The representation of women in this sample reflects the current demographics of HIV in Canada, where it is estimated that only approximately 25% of people living with HIV are women (Public Health Agency of Canada, 2020), and fewer still in the specific clinics that served as the recruitment sources for the BHN cohort. In addition, women living with HIV in Canada are less likely to participate in research studies, for a variety of reasons (Mayo et al., 2018). Second, this sample, by design, was made up of people with well-controlled HIV. There are reasons to expect differences in brain health in people with poor viral control, which may be associated with ongoing virally-mediated brain injury (O'Connor & Zeffiro, 2019; Sanford, Ances, et al., 2018). A further limitation of this study is that the sample size was set for the two BHN sub-studies from which the current work drew, not for this particular study. However, the sample available is larger than most studies in the existing reward processing EEG literature in clinical groups. Post hoc sample size calculations show that this sample was adequate to detect medium effect sizes in the relationships between the ERPs of interest of this study and meaningful activity with age included as a covariate.

In summary, we found preliminary evidence to support a link between brain responses to feedback measured by FB-P3 and real-world motivated behavior in older people living with

chronic HIV infection. In line with a previous study in healthy individuals, the FB-P3 but not the RewP was linked to motivated behavior. This was the first study to demonstrate that RewP and FB-P3 ERPs are reliably present in people with HIV, with the expected distinctions between gain and loss feedback whether using single electrodes or clusters. Self-reported motivation measured with items from a widely used apathy scale was not linked to any of the EEG correlates of feedback, which may point to problems with the apathy scale, at least for the purposes of studying neural correlates of motivation in HIV. The results here suggest that a promising approach for further neuroscience research on this clinical syndrome might be to focus on observable motivated behaviors (whether self-reported or clinician-observed) rather than on apathy questionnaires. The FB-P3 has promise as a potential EEG biomarker of motivation, independent of age or nadir CD4 status in HIV. Further work is needed to replicate this result, study the underlying mechanisms, and establish the utility of this EEG marker as a potential biomarker for diagnosis or assessing the effects of interventions to improve motivation in people living with HIV.

Notes

We thank Christine Déry and Susan Scott for their help with participant recruitment and data analysis, Marcus Sefranek for technical assistance, and the Positive Brain Health Now investigators, research staff, and participants. This work was supported by a grant from the Velux Foundation with support from the Brain@McGill programme and the Healthy Brains for Healthy Lives CFREF grant to McGill University, the Canadian Institutes of Health Research (CIHR) (TCO-125272), and the HIV Clinical Trials Network (CTN 273; CTN-026).

Supplementary Material

Supplementary Table 5.1

Multiple linear regressions predicting motivation (SAS-R)

Outcome: SAS-R, 52.04 (13.83) **Predictors**	**Parameter Estimate (*β*)**	**Standard Error**	**95 % CI (lower bound, upper bound)**	**R^2**
RewP amplitude, µV	0.06	0.04	(-0.03, 0.14)	
Age, decades	-0.21	0.15	(-0.52, 0.10)	0.06
FB-P3 amplitude, µV	0.04	0.03	(-0.02, 0.10)	
Age, decades	-0.19	0.16	(-0.50, 0.13)	0.05
N1 amplitude, µV	0.28	0.68	(-1.078 1.65)	
Age, decades	-5.62	2.26	(-10.13, -1.10)	0.09

Note: Results are from clusters centered at FCz for RewP and at Pz for FB-P3 gain feedback conditional averages. To facilitate interpretation age is expressed in decades. A logit transformation was applied to SAS-R $^{*}p < 0.05$; $^{**}p < 0.01$; ***p < 0.001.

Supplementary Table 5.2

Multiple linear regressions predicting motivation (SAS-R)

Outcome: SAS-R, 52.04 (13.83) **Predictors**	**Parameter Estimate (*β*)**	**Standard Error**	**95 % CI (lower bound, upper bound)**	**R^2**
Loss feedback				
RewP amplitude, µV	0.79	0.65	(-0.50, 2.09)	
Age, decades	-5.76	2.20	(-10.15, -1.46)	0.11
FB-P3 amplitude, µV	0.56	0.45	(-0.34, 1.46)	
Age, decades	-5.43	2.23	(-9.88, -0.97)	0.11
N1 amplitude, µV	0.23	0.54	(-0.84, 1.30)	
Age, decades	-5.47	2.36	(-10.17, -0.77)	0.09
Difference (loss-gain)				
ΔRewP, µV	0.34	1.49	(-2.63, 3.32)	
Age, decades	-6.00	2.27	(-10.52, -1.48)	0.09

Note: Results are from a cluster centered at FCz for RewP and a cluster centered at Pz for FB-P3 loss feedback conditional averages. The ΔRewP is calculated as the difference between loss

minus gain feedback, the results shown here are from FCz. To facilitate interpretation age is expressed in decades. A logit transformation was applied to SAS-R $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$

Supplementary Table 5.3

Multiple linear regressions predicting ERP amplitudes

Outcome, mean (SD), μV Predictors	Parameter Estimate (*β*)	Standard Error	95 % CI (lower bound, upper bound)	R^2
		Gain feedback		
RewP amplitude, 2.91 (2.39)				
Nadir CD4, 100 cells/μL	-0.21	0.18	(-0.57, 0.14)	
Age, decades	-0.54	0.40	(-1.33, 0.25)	0.04
FB-P3 amplitude, 6.77 (3.54)				
Nadir CD4, 100 cells/μL	-0.47	0.26	(-0.98, 0.05)	
Age, decades	-1.21*	0.58	(-2.36, -0.06)	0.09*
N1 amplitude, -1.70 (2.33)				
Nadir CD4, 100 cells/μL	0.02	0.17	(-0.32, 0.37)	
Age, decades	-0.65	0.39	(-1.42, 0.13)	0.04
		Loss feedback		
RewP amplitude, 2.18 (2.38)				
Nadir CD4, 100 cells/μL	-0.09	0.18	(-0.45, 0.27)	
Age, decades	-0.22	0.40	(-1.02, 0.58)	-0.02
FB-P3 amplitude, 6.20 (3.45)				
Nadir CD4, 100 cells/μL	-0.39	0.25	(-0.90, 0.12)	
Age, decades	-0.94	0.57	(-2.08, 0.20)	0.04
N1 amplitude, -1.06 (3.08)				
Nadir CD4, 100 cells/μL	0.02	0.17	(-0.32, 0.37)	
Age, decades	-0.65	0.39	(-1.42, 0.13)	0.04
		Difference (loss-gain)		
ΔRewP, -0.73 (1.06)				
Nadir CD4, 100 cells/μL	0.12	0.08	(-0.03, 0.28)	
Age, decades	**0.32**	**0.17**	**(-0.03, 0.66)**	**0.04**

Note: Results are from clusters centered at FCz for RewP and at Pz for FB-P3 . To facilitate interpretation, age is expressed in decades, and nadir CD4 count in 100 cells/µL. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$.

Chapter 6

General Discussion

Chapter 6

General Discussion

Motivation is a key component of successful aging, while a lack of motivation, on its own or together with other features of the apathy syndrome, is considered a risk factor for mortality, cognitive decline, dementia, frailty, and medication non-adherence (Hölttä et al., 2012; Semprini et al., 2012; Willem van Dalen et al., 2018). Despite the prevalence of motivational deficits in several chronic neurological, psychiatric, and medical disorders, as well as in otherwise healthy older people (Fervaha et al., 2015; Nobis, 2018; Reekum et al., 2005; S. E. Starkstein, Fedoroff, Price, Leiguarda, & Robinson, 1993), little is known about the underlying mechanisms of motivation. While it is generally accepted that there are behavioral, cognitive, and emotional domains of apathy, in this work, in keeping with the cognitive neuroscience approach to motivation to date, we focused on the behavioral domain.

Cognitive neuroscience frameworks aim to define aspects of motivation at the level of neurobiologically-meaningful component processes (D. M Barch et al., 2019; Fellows, 2004a; Husain & Roiser, 2018). The three original studies presented in this thesis focused on some of these hypothesized components of motivation: effort, reward, and response to feedback. This thesis sought to provide evidence for a relationship between laboratory tasks or their neural

correlates, and self-reported measures of real-world motivation. In all three studies, real-world motivation was assessed with items from the Starkstein Apathy Scale (S. . E. Starkstein & Leentjens, 2008; S. . Starkstein et al., 1992). In addition, in the two projects that sampled from the Brain Health Now cohort, a second real-world measure was available that is arguably a more straightforward indicator of motivation: i.e., the number of hours spent on goal-directed, and thus in some sense "meaningful", activities.

Specific Contributions

This work aimed to contribute to the understanding of the construct of motivation and possibly new approaches to the diagnosis of apathy in the clinic. The specific contributions of this thesis were:

1) The subjective cost of effort measured with an ECDM task was associated with self-reported real-world motivation as indexed by the number of hours spent on meaningful activities in older people with well-controlled HIV infection. This association was not present for motivation measured with items from the SAS.

2) The subjective cost of effort measured with two different ECDM tasks was not associated with motivation as assessed by items from the SAS in community-dwelling older adults.

3) Performance on these two ECDM tasks was not correlated in the community-dwelling older sample.

4) The late evoked potential elicited by feedback in a guessing task, the FB-P3, was associated with self-reported real-world motivation in older people with well-controlled HIV infection as indexed by the number of hours spent on meaningful activities. This association

was not present for an earlier ERP, the RewP, or with motivation measured with items from the SAS.

This work was conducted in three different samples relevant to clinical apathy: older people from the community, and older people living with well-controlled HIV. The samples were large by the standards of this emerging literature. There was a wide range of apathy symptoms and motivated behavior. Selection bias may be a particular issue for studies of motivation, as those with less motivation may not participate in research. A strength of the work here was the use of sequential recruitment, where possible, to reduce selection bias. Further, we leveraged the data available from the whole BHN cohort to assess the potential for such bias in Chapter 3, comparing individuals who agreed to participate in our study with those who refused. Reassuringly, refusers were not less motivated, nor did they have more symptoms of other indicators of brain health compared to those who participated.

HAND classification was not used in the HIV samples here, as our research group has identified several limitations to this conventional clinical diagnostic approach (Antinori et al., 2007; M.-J. Brouillette et al., 2021). In addition to wide variability in how the criteria are operationalized across studies, this categorical approach conveys less information compared to a continuous approach (Mayo et al., 2016). Instead, the studies presented in this thesis report on global cognitive performance using a short test battery, BCAM (Brouillette et al., 2015). We note also that people with clinically evident dementia were excluded from the BHN cohort, so were not studied here.

Motivation Indicated by Real-World Self-Directed Activity.

Existing studies that found associations between ECDM and apathy symptoms used a variety of apathy scales (see Table 4.1). There has been no work on whether these scales align; they vary substantially in item content, often mixing beliefs (e.g. "I often need a push to get started…") and actions. The LARS, one of the most widely used scales for apathy, especially in PD studies, has items that are more related to real-world self-directed activity than the items of the SAS. LARS items are thus more closely related to our measure of hours spent on meaningful activity. Some examples of these LARS items are: *What do you do during the day? What do you do to keep yourself occupied, and then how many times a week do you do that?* (Sockeel et al., 2006). It is perhaps not surprising that a focus on actions rather than beliefs seems to be more related to laboratory decisions and neural responses, both in the work presented here and in the wider literature. These observations could guide future research on the neural basis of apathy and motivation.

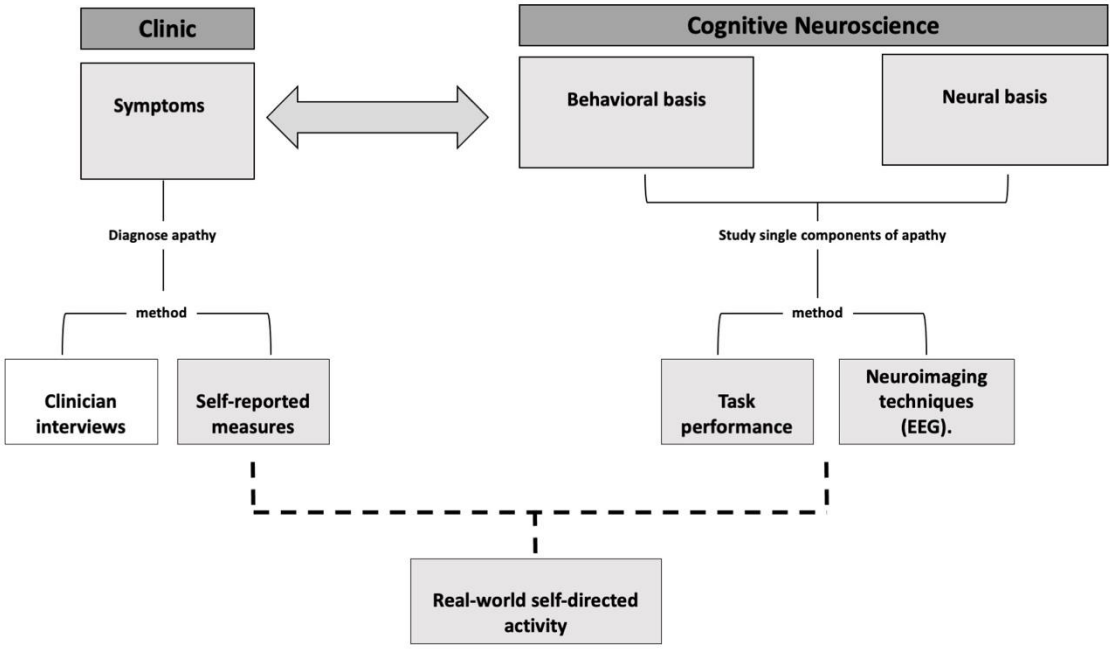
The present work provided evidence that there is a link between time spent on meaningful activities and laboratory tasks of motivation. Reduced behavior aimed towards a goal or completion of a task is part of the diagnostic criteria of apathy (Mann, 1990; Marin & Wilkosz, 2005b; Robert et al., 2018). Thus, motivation is required for engagement in goal-directed behaviors (Marin & Wilkosz, 2005b). However, meaningful activity requires more than motivation. Reduced engagement in meaningful activities could also be due to difficulties in other capacities or to external factors unrelated to neurobehavioral considerations (e.g. restriction of time, having other responsibilities, physical restrictions) as well as difficulty in recalling and thus reporting such activities. In this work, meaningful activity and SAS-R scores

were not correlated in either of the samples that completed both scales. However, these two measures were related in the full BHN cohort (n=856) (Mayo et al., 2020).

Future work could use assessment of real-world self-directed activities such as the number of hours spent doing meaningful activities to optimize the psychometrics of current self-report assessments of motivation. Figure 6.1 shows a diagram of the different methods used in the clinic and in cognitive neuroscience to study apathy. In grey are the methods used in this thesis. This diagram also shows meaningful activity as a potential outcome measure that could bridge the gap between the clinic and neuroscientific research.

Figure 6.1

Schematic framework showing real-world self-directed activity as a bridge outcome measure between clinical and cognitive neuroscientific approaches to apathy.



Note: The different methods used in this thesis are presented in grey. Real-world self-directed activity is an index of motivation that in this thesis was related to laboratory task performance measures of motivation and an EEG measure of feedback processing.

Improving the Starkstein Apathy Scale.

As outlined in the Introduction, the original SAS has some psychometric limitations at the item level (Hum et al., 2021; Lourenço, 2014). Rasch analysis can reduce some of these limitations by identifying the poorly functioning items and clarifying if the remaining items

measure one or more underlying constructs. In this work, we used items drawn from the SAS, selected based on Rasch analysis in parallel work. In the HIV sample, we used 8 items from the SAS, while for the study conducted in community-dwelling older people, we retained all but one item from the original 14-item scale (Figure 7.3). These choices reflected the state of knowledge at the time each study was designed. The principle underlying Rasch analysis is that items are assessing a single construct, such that the construct can be measured (with varying precision) even if only some items are administered. Further, the Rasch model assumes unidimensionality, which means that all items that fit the model will measure a single construct and will be independent of each other (Bond, T. G., & Fox, 2013; Choi, Mericle, & Harachi, 2006; Smith, 2004). Thus, at least in principle, the same latent construct was assessed in all three studies. In practice, the varying items makes it hard to make definitive comparisons across studies. Nonetheless, as discussed above, we suggest that the Starkstein Apathy Scale would benefit from further psychometric optimization, or perhaps should be replaced by questions focusing solely on actual real-world motivated activities. These findings, together with the lack of evidence for convergent validity with ECDM in the two studies reported here, and with real-world self-directed behavior in the HIV+ sample, suggest that further work is needed to optimize self-report of motivation in older adults and people with HIV, if not in general.

Effort Cost Decision Making as a Laboratory Measure of Motivation.

There is evidence in schizophrenia, PD, and healthy young people of a link between low motivation and reduced willingness to exert effort in exchange for reward measured with ECDM tasks (Chong, Bonnelle, & Husain, 2016; Chong et al., 2015; Culbreth, Moran, & Barch, 2017; Horan et al., 2015; Huang et al., 2016; Le Bouc et al., 2016; Zénon et al., 2016). Although

we used similar ECDM tasks, we did not replicate the reported relationships in older people with or without HIV infection with motivation indexed by items from the SAS. However, we did find a relationship with real-world activity.

One consideration was whether the ECDM tasks we used effectively assessed the intended construct, in a manner comparable to similar tasks in the literature. Some of the ECDM tasks found in the literature required higher levels of effort over an extended time than the version we used. This possible explanation was tested to some extent by the study described in Chapter 4, in which changes were made to the handgrip ECDM task to bring it closer to those used in the literature, and the EEfRT task was added. The EEfRT is widely used and is recommended by the NIH Research Domain Criteria Initiative as a measure of effort cost. Given that we again found no association between self-reported motivation (SAS-R) and either ECDM measure in either task, it seems unlikely this is entirely explained by task characteristics.

Chapter 4 also took a critical look at the ECDM task used in the first study (Chapter 3), testing convergent validity with the better-established EEfRT. We found that performance on these two tasks did not correlate and thus they cannot be used interchangeably, at least in older people. There are several differences between these tasks, and it is possible that participants were using different strategies in each. While both purport to measure the subjective cost of effort, we observed that some participants had an increased acceptance of the highest effort levels in the ECDM task (handgrip) but a reduced acceptance of high effort in the EEfRT. Effort was experienced on every trial in the EEfRT, and there is also a need to consider risk in that task. Further, the handgrip ECDM task and the EEfRT pose different questions. The former asks: Are you willing to make a particular effort in exchange for a

particular monetary reward? Whereas the EEfRT asks: Are you willing to make less effort for a fixed monetary amount OR more effort for a larger amount? That is, in the EEfRT, participants always had to make some effort, while in the handgrip task, participants had the option to not make effort at all if the offer was considered not worth it. They could wait and only accept those options with the highest reward value or accept a lower value option and gamble that they would not have to make the effort (since only one trial was executed at the end of each block). Whereas in the EEfRT, participants always had to make effort; maybe some participants decided to save energy.

An additional consideration of these two ECDM measures is that a substantial minority of older participants were unwilling or unable to complete the EEfRT, whereas all participants completed the handgrip ECDM task. Adding a calibration phase at the beginning of the EEfRT or substituting handgrip effort for the button presses might help make it more accessible to older people with arthritis or reduced dexterity.

As mentioned at the beginning of this section, although we used ECDM tasks similar to those in other studies, we did not find relationships between these tasks and motivation (SAS-R) in older people with or without HIV infection. Most of the current evidence for a link between ECDM performance and apathy is in PD and schizophrenia, two conditions in which apathy is thought to relate to dopamine pathology (T. T.-J. Chong et al., 2015; T. T.-J. T. J. Chong et al., 2016; Culbreth et al., 2018; Horan et al., 2015; Huang et al., 2016; Le Bouc et al., 2016; Zénon et al., 2016). This was the first study assessing ECDM in an HIV+ sample. There are only two ECDM studies in samples that might be considered more similar to people living with HIV. One study was in healthy individuals after administration of lipopolysaccharide (LPS) to

investigate the effects of acute inflammation on ECDM, fatigue, and depression (Draper et al., 2018), and another study was in cancer patients to investigate the relationship between ECDM and fatigue (Lacourt et al., 2018). While these studies did not include a measure of apathy, they also found no evidence for hypothesized associations between ECDM performance and other brain health measures (depression, fatigue).

The lack of association between SAS-R scores and ECDM performance observed in both an HIV+ and an elderly sample across the studies described in Chapters 3 and 4, in the context of the wider literature, suggests that any relationship is either condition-specific or that there is at most a weak relationship, perhaps due to the previously discussed problems with the SAS items.

Motivation Beyond Effort-Cost Decision Making.

Overall a further consideration of the studies investigating motivation is whether laboratory tasks assessing motivation, such as ECDM tasks, are too narrowly focused on explicit considerations of external rewards. Psychological research on motivation argues that there may be multiple other aspects of motivation, such as behaviour driven by novelty-seeking and curiosity rather than by monetary amounts. Perhaps this is as, or more, important for understanding disordered motivation in clinical populations. However, there are no established tests of these constructs. We tested one candidate task, adapted from the intrinsic motivation literature to require a trade-off between curiosity and effort. We did not see a statistically significant association initiating the task or the number of trials completed, and SAS-R. This was an exploratory study with a limited sample size, and as discussed above, we have concerns about the validity of the SAS-R. Unfortunately, in that study, we did not collect data on real-

world activities. More work is needed to fine-tune the task and test its relevance to clinical constructs and everyday behaviors.

As described in the Introduction, the existing cognitive neuroscience frameworks of motivation propose ECDM as a component process of motivation but also propose other components such as *interaction with the goal*. The study presented in Chapter 5 focused on the brain response to feedback as a correlate of motivation. Given the results of the other two studies, we used meaningful activities as a primary outcome and SAS-R as a secondary outcome measure of motivation. We hypothesized that response to positive feedback in the ERPs of interest would relate to meaningful activities. We found that the response to both positive and negative feedback predicted meaningful activity. We specifically found that a late EEG correlate of reward processing: the FB-P3, and not the RewP, was linked to number of hours of meaningful activity. While there are many studies relating EEG components evoked in response to feedback (i.e. particularly the RewP) to symptoms of depression (Proudfit, Bress, Foti, Kujawa, & Klein, 2015), to our knowledge this was the first study in HIV to investigate whether these ERPs are related to self-reported motivation.

One of the main limitations of the EEG literature, in general, is the diverse methods used to measure the same ERPs. We carried out a literature review to establish the most appropriate methods and pre-registered the analysis of this study, an approach with several advantages (Head, Holman, Lanfear, Kahn, & Jennions, 2015). Publicly registering the hypotheses limits the analysis to the ones planned a-priori, thus limiting additional analysis which might yield spurious statistically significant results (so-called p-hacking).

EEG also has advantages, including its relatively low cost compared to other neuroimaging methods. In principle, this makes EEG a method more readily transferable to the clinic, particularly in resource-poor settings. Moreover, previous work from our group has demonstrated advantages of EEG in detecting subtle brain dysfunction in HIV, showing that it is more informative than structural MRI (Cruz, 2019).

Limitations

This work has limitations. The measure of real-world engagement in meaningful activities was only available for the two HIV studies (Chapters 3 and 5) as it was part of the BHN cohort dataset; we drew on it to address the concerns that emerged as we scrutinized the SAS results. We were unfortunately not able to add it to the study described in Chapter 4, as data collection was already well underway when the results of the first study became available. All studies included items of the SAS which were selected based on Rasch analysis. However, this work was being carried out by others, with adjustments ongoing as these studies were carried out. This led to a different number of items on the SAS-R used in the two HIV studies (see Figure 7.3). Nevertheless, this is unlikely to have substantially affected the results, given the principles of Rasch analysis.

A further limitation of the ECDM studies is that perhaps participants did not allocate their true maximum contraction during the calibration period of the ECDM tasks (handgrip), which could have resulted in a reduced maximum voluntary contraction (MVC) value. This could be addressed in future studies by having participants do more trials during the calibration period, or taking the maximum value obtained as opposed to the mean value of their two MVC,

which is the method we followed, as has been done in the literature (T. T.-J. Chong et al., 2015; T. T.-J. T. J. Chong et al., 2016).

Although this work involved amongst the largest samples published so far using an ECDM task, samples were still perhaps too small to detect small effect sizes between self-reported brain health indicators and performance task measures of ECDM. The findings from Chapters 3 and 5 had moderate effect sizes, similar to the effects reported in other published studies.

We did not carry out conventional correction for multiple comparisons in these studies, which means that Type I error needs to be considered. We took steps to mitigate this: all findings presented in this work included 95% confidence intervals, which replaces p-values and does not require a correction for multiple comparisons (Tan & Tan, 2010). The main analyses in Chapter 3 and 4 were hypothesis-driven and planned a priori, providing further protection against spurious findings. Additional analyses were clearly reported as exploratory and require replication. Finally, all analyses conducted in Chapter 5 were planned and preregistered (https://osf.io/yemhn).

There were few women in the two HIV studies. This is representative of the current demographics of HIV in Canada (Public Health Agency of Canada, 2020), exacerbated by lower rates of participation in research studies for women living with HIV in Canada (Mayo et al., 2018). The community-dwelling older adult sample included more women and suggested that sex differences are unlikely to be present in ECDM tasks. More work is needed to address potential sex or gender effects on motivation and its neural correlates.

Future Directions

As outlined in the introduction of this thesis, there has been little work in bridging the gap between the clinic and neuroscientific research on motivation. Our findings show that real-world self-directed activities are more related than items from a widely used apathy scale to laboratory measures of motivation, and an EEG correlate of feedback processing. Future studies could extend this work by studying other components of decision-making, such as option generation, reward anticipation, and action initiation (D. M Barch et al., 2019; Fellows, 2004a; Husain & Roiser, 2018), which might also be important in understanding real-world motivation.

While our studies relating laboratory measures to real-world self-directed activities were in people living with HIV, our findings suggest that the results can be generalized to older people in general. We chose people living with HIV as the main focus because of the high incidence of motivational deficits, amongst a range of other mental health and neurological symptoms (i.e. fatigue, depression, neurocognitive impairment) (Cruz, 2019; Cysique & Brew, 2019; Kamat et al., 2012). Thus, participants with HIV constitute an informative sample to study the strength and specificity of self-reported measures of real-world motivation and laboratory and neural measures.

Considering the promising findings of a relationship between the FB-P3 and real-world activity, more work is warranted. A first step would be to relate this ERP to measures of motivation in other clinical samples to address the specificity to HIV. Identifying the neural substrates of the FB-P3 using source localization methods would help to better distinguish this ERP from other similar ERPs like the P300 evoked by oddball tasks, which has also been related to apathy in other conditions (S.C. Kleih et al., 2010; Sonja C. Kleih & Kubler, 2013; Mathis et al., 2014; Yamagata et al., 2004). An fMRI-EEG study might be a useful next step. While we did not

find a significant association with the RewP in this work, this ERP could be another EEG component worth studying further. Methodological improvements are possible: This task could include monetary rewards in addition to feedback, as well as "boost" trials that elicit enhanced RewP responses (Gehring, 2002; Holroyd, Larsen, & Cohen, 2004; Martinez-Horta et al., 2014).

As mentioned in the Introduction, it is unclear whether apathy is a direct effect of HIV infection on brain function. Here, variation in the FB-P3 was not explained by past immunosuppression (i.e. related to HIV severity). However, in another study from our group in a subset of the same sample, variation of the oddball-P300 was explained by nadir CD4, and the P300 amplitude was in turn related to thalamic volumes (Fernandez Cruz et al., 2021). These differences might relate to different neural circuits underlying feedback responses and oddball responses, with the latter circuit perhaps more susceptible to viral damage. Other factors, such as co-morbities, substance use, or cerebrovascular injury might explain the variation in both motivation and FB-P3 amplitude observed in this study.

The findings presented in this thesis have potential clinical applications. More work will be needed to isolate the motivational element of meaningful activities from other capacities or external factors unrelated to neurobehavioral considerations (i.e. time, cognition, etc.) to improve the specificity of this real-world indicator. In addition, to facilitate the use of EEG in the clinic, it will be important to determine whether a shorter version of the guessing task is adequate. It will be also important to determine whether a minimal number of electrodes can identify the FB-P3. Here we used a 256 high-density EEG, which is not ideal for clinical application. More generally, replication in other, diverse samples, will be important.

Conclusions

This work asked whether effort and reward processes are related to measures of real-world motivation in two samples of HIV+ individuals, and one sample of community-dwelling older adults. We found evidence that ECDM tasks may relate to real-world motivation in these conditions, but also that the psychometric characteristics of these tasks can be further improved. We also identified a promising candidate EEG biomarker for motivation.

Chapter 7

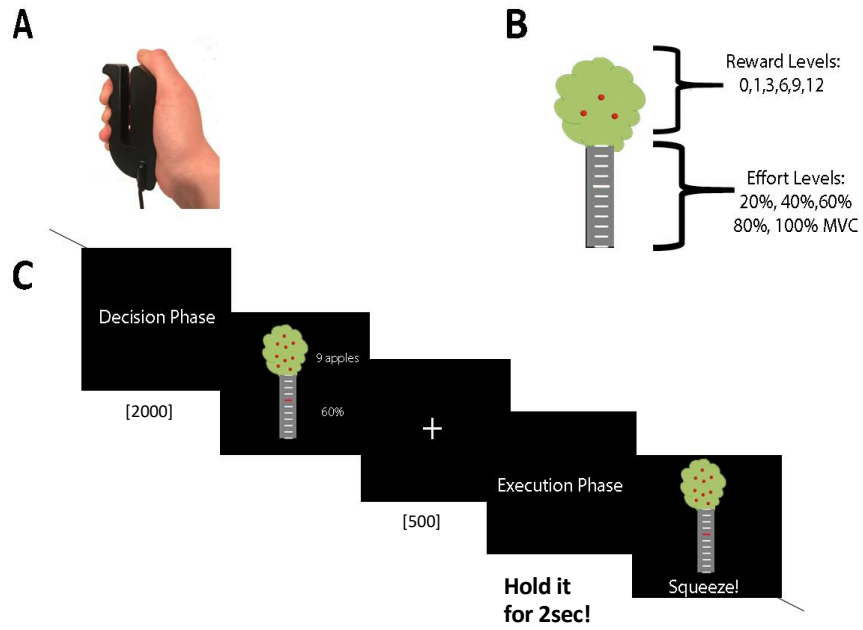
Appendices

Supplementary Material for Chapter 4

Appendix I

Figure 7.1

Schematic diagram of a single trial of the Handgrip effort cost decision making task (after adjustments).



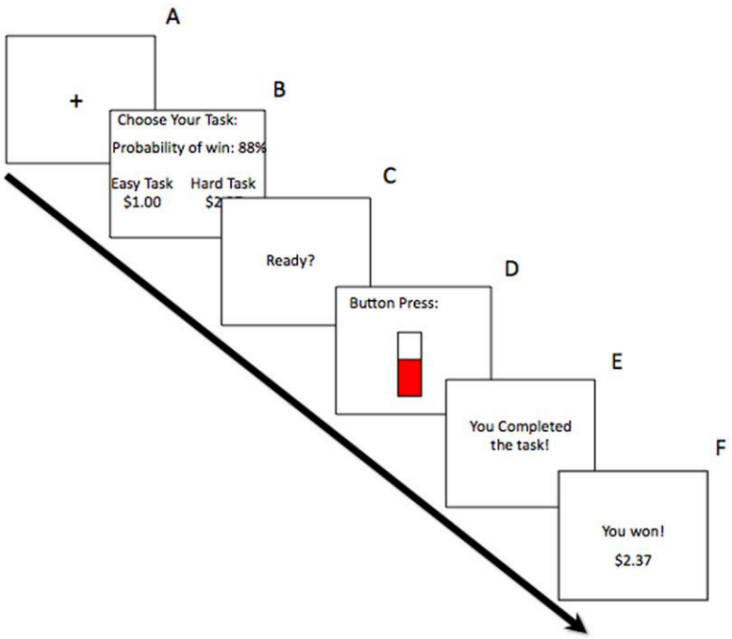
Note: A). Handgrip participants used to exert force in the task. (B) Summary of all possible effort-reward combinations seen in the task, and an example of the apple tree graphic used to convey these combinations. (C). Example of a decision phase trial with execution phase. After each decision block participants were presented with an execution phase trial, in which an

option from the previous block, selected at random, was presented. If they had accepted the choice selected, they were asked to press the handgrip and hold the required for 2 seconds. If they had rejected the choice selected, they waited 2 seconds for the next block to continue. Modified task version of (Bonnelle, Veromann, et al., 2015).

Appendix II.

Figure 7.2

Schematic diagram of a single trial of the Effort Expenditure for Rewards Task (EEfRT) developed by Treadway (2009)



Note: B) Participants choose from two effort options (high effort & high reward vs low effort and low reward) during a 5s period. C) A sign is presented to participants for 7s, in preparation of effort. D) Participants are then required to begin the button presses correspondent to their previous selection. A random effort is selected, if no effort selection was made in the previous

trial. E) Feedback is given to participants on whether they completed the required button presses. F) Additional feedback is given to participants on whether they receive the monetary reward associated with the probability. Image from (Treadway et al., 2009)

Supplementary Material for Chapter 3-5

Appendix III.

Table 7.1

Items used to assess self-reported motivation.

Starkstein Apathy Scale	Apathy domain	SAS-R items used in HIV (Chapter 3)	SAS-R items used in HIV (Chapter 5)	SAS-R items used in healthy older people (Chapter 4)
1. Are you interested in learning new things	**Cognitive**	***kept***	***kept***	***kept***
2. Does anything interest you?	**Cognitive**	***kept***	***kept***	***kept***
3. Are you concerned about your condition?	**Other**	*removed*	*removed*	*removed*
4. Do you put much effort in to things?	**Behavior**	***kept***	*removed*	***kept***
5. Are you always looking for something to do?	**Behavior**	*removed*	***kept***	***kept***
6. Do you have plans and goals for the future?	**Cognitive**	***kept***	*removed*	***kept***
7. Do you have motivation?	**Behavior**	***kept***	***kept***	***kept***
8. Do you have energy for daily activities?	**Behavior**	***kept***	***kept***	***kept***
9. Does someone have to tell you what to do each day?	**Behavior**	*removed*	***kept***	***kept***
10. Are you indifferent to things?	**Emotion**	*removed*	***kept***	***kept***
11. Are you unconcerned with many things?	**Cognitive**	*removed*	*removed*	***kept***
12. Do you need a push to get started on things?	**Behavior**	*removed*	***kept***	***kept***
13. Are you neither happy nor sad, just in between?	**Emotion**	*removed*	*removed*	***kept***
14. Would you consider yourself apathetic?	**Other**	*removed*	*removed*	***Kept***
Not at all slightly some a lot				

Note: From left to right, items of the original Starkstein Apathy Scale (Starkstein et al. 1992). Each item and apathy domain correspondences (Pedersen et al., 2012). SAS-R items used in Chapter 3, items were derived from work by our group as an exploratory initial Rasch analysis conducted in stroke patients (Lourenço, 2014). SAS-R items used in Chapter5; items were derived from a Rasch analysis performed by members of our group in the same sample used in the study presented in Chapter 5. SAS-R items used in Chapter 4; items were derived from a

Rasch analysis performed by members of our group in the same sample used in the study presented in Chapter 4.

Table 7.2

Items used to assess meaningful activities.

Which of the activities do you do regularly? If yes, how many hours in a typical week?

	NO	YES	If YES, numbers of hours per week.
1. Reading			
2. Checking e-mail			
3. Surfing the internet			
4. Work on computer			
5. Games on computer			
6. Crafts/hobbies			
7. Other: _____			

Bibliography

Ances, B. M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent Effects of HIV, Aging, and HAART on Brain Volumetric Measures. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *59*(5), 469. doi: 10.1097/QAI.0B013E318249DB17

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., … Wojna, V. E. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789–1799. doi: 10.1212/01.WNL.0000287431.88658.8b

Askari, S., Fellows, L. K., Brouillette, M. J., & Mayo, N. E. (2020). Development and validation of a voice-of-the-patient measure of cognitive concerns experienced by people living with HIV. *Quality of Life Research*, (0123456789). doi: 10.1007/s11136-020-02679-z

Bäckman, L., Lindenberger, U., Li, S. C., & Nyberg, L. (2010). Linking cognitive aging to alterations in dopamine neurotransmitter functioning: Recent data and future avenues. *Neuroscience & Biobehavioral Reviews*, *34*(5), 670–677. doi: 10.1016/J.NEUBIOREV.2009.12.008

Balconi, M., & Crivelli, D. (2010). FRN and P300 ERP effect modulation in response to feedback sensitivity: The contribution of punishment-reward system (BIS/BAS) and Behaviour Identification of action. *Neuroscience Research*, *66*(2), 162–172. doi: 10.1016/j.neures.2009.10.011

Barch, D. M., Pagliaccio, D., Luking, K., Moran, E. K., & Culbreth, A. J. (2019). Pathways to motivational impairments in psychopathology: Common versus unique elements across domains. In M. Neta & I. J. Haas (Eds.), *Emotion in the Mind and Body* (pp. 121–160). doi: 10.1007/978-3-030-27473-3_5

Barch, D. M., Treadway, M. T., & Schoen, N. (2014). Effort, anhedonia, and function in schizophrenia: Reduced effort allocation predicts amotivation and functional impairment. *Journal of Abnormal Psychology*, *123*(2), 387–397. doi: 10.1037/a0036299

Barclay, T. R., Hinkin, C. H., Castellon, S. A., Mason, K. I., Reinhard, M. J., Marion, S. D., … Durvasula, R. S. (2007). Age-associated predictors of medication adherence in HIV-positive adults: Health beliefs, self-efficacy, and neurocognitive status. *Health Psychology*, *26*(1),

40–49. doi: 10.1037/0278-6133.26.1.40

Barry, T. J., Griffith, J. W., De Rossi, S., & Hermans, D. (2014). Meet the Fribbles: novel stimuli for use within behavioural research. *Frontiers in Psychology*, *5*, 103. doi: 10.3389/fpsyg.2014.00103

Belden, A. C., Irvin, K., Hajcak, G., Kappenman, E. S., Kelly, D., Karlow, S., … Barch, D. M. (2016). Neural Correlates of Reward Processing in Depressed and Healthy Preschool-Age Children. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(12), 1081–1089. doi: 10.1016/j.jaac.2016.09.503

Bergé, D., Pretus, C., Guell, X., Pous, A., Arcos, A., Pérez, V., & Vilarroya, O. (2018). Reduced willingness to invest effort in schizophrenia with high negative symptoms regardless of reward stimulus presentation and reward value. *Comprehensive Psychiatry*, *87*, 153–160. doi: 10.1016/j.comppsych.2018.10.010

Blanchard, J. J., & Cohen, A. S. (2006). The Structure of Negative Symptoms Within Schizophrenia: Implications for Assessment. *Schizophrenia Bulletin*, *32*(2), 238–245. doi: 10.1093/schbul/sbj013

Boban, J., Thurnher, M. M., & Kozic, D. (2021). Brain aging in HIV and retrovirals. In *Assessments, Treatments and Modeling in Aging and Neurological Disease* (pp. 203–212). doi: 10.1016/B978-0-12-818000-6.00019-6

Bock, M. A., Bahorik, A., Brenowitz, W. D., & Yaffe, K. (2020). Apathy and risk of probable incident dementia among community-dwelling older adults. *Neurology*, *95*(24), e3280–e3287. doi: 10.1212/WNL.0000000000010951

Bond, T. G., & Fox, C. M. (2013). *Applying the Rasch model: Fundamental measurement in the human sciences. Psychology Press*. Psychology Press.

Bonnelle, V., Manohar, S., Behrens, T., & Husain, M. (2015). Individual Differences in Premotor Brain Systems Underlie Behavioral Apathy. *Cerebral Cortex*, bhv247. doi: 10.1093/cercor/bhv247

Bonnelle, V., Veromann, K.-R., Burnett Heyes, S., Lo Sterzo, E., Manohar, S., & Husain, M. (2015). Characterization of reward and effort mechanisms in apathy. *Journal of Physiology-Paris*, *109*(1–3), 16–26. doi: 10.1016/j.jphysparis.2014.04.002

Brew, B. J., Crowe, S. M., Landay, A., Cysique, L. A., & Guillemin, G. (2009). Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*, *4*(2), 163–174. doi: 10.1007/s11481-008-9143-1

Brouillette, M.-J., Koski, L., Forcellino, L., Gasparri, J., Brew, B. J., Fellows, L. K., … Cysique, L. A. (2021). Predicting occupational outcomes from neuropsychological test performance in older people with HIV. *AIDS*, *35*(11), 1765–1774. doi: 10.1097/QAD.0000000000002927

Brouillette, M. J., Fellows, L. K., Palladini, L., Finch, L., Thomas, R., & Mayo, N. E. (2015). Quantifying cognition at the bedside: A novel approach combining cognitive symptoms and signs in HIV. *BMC Neurology*, *15*(1). doi: 10.1186/s12883-015-0483-1

Brower, K. J., Maddahian, E., Blow, F. C., & Beresford, T. P. (1988). A comparison of self-reported symptoms and DSM-III-R criteria for cocaine withdrawal. *American Journal of Drug and Alcohol Abuse*, *14*(3), 347–356. doi: 10.3109/00952998809001556

Brown, D. R., Richardson, S. P., & Cavanagh, J. F. (2020). An EEG marker of reward processing is diminished in Parkinson's disease. *Brain Research*, *1727*(September 2019), 146541. doi: 10.1016/j.brainres.2019.146541

Castaneda, G., Fernandez Cruz, A.-L., Sefranek, M., Yau, Y. H. ., Brouillette, M.-J., Mayo, N. E., & Fellows, L. K. (2021). Does Effort-Cost Decision-Making Relate to Real-World Motivation in People Living with HIV? *Manuscript Submitted for Publication*.

Castellon, S. A., Hinkin, C. H., Wood, S., & Yarema, K. T. (1998). Apathy, depression, and cognitive performance in HIV-1 infection. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 320–329. doi: 10.1176/jnp.10.3.320

Cerasoli, C. P., Nicklin, J. M., & Ford, M. T. (2014). Intrinsic motivation and extrinsic incentives jointly predict performance: A 40-year meta-analysis. *Psychological Bulletin*, *140*(4), 980–1008. doi: 10.1037/a0035661

Chang, W. C., Westbrook, A., Strauss, G. P., Chu, A. O. K., Chong, C. S. Y., Siu, C. M. W., … Chen, E. Y. H. (2020). Abnormal cognitive effort allocation and its association with amotivation in first-episode psychosis. *Psychological Medicine*, *50*(15), 2599–2609. doi: 10.1017/S0033291719002769

Chang, Wing Chung, Chu, A. O. K., Treadway, M. T., Strauss, G. P., Chan, S. K. W., Lee, E. H. M.,

… Chen, E. Y. H. (2019). Effort-based decision-making impairment in patients with clinically-stabilized first-episode psychosis and its relationship with amotivation and psychosocial functioning. *European Neuropsychopharmacology*, *29*(5), 629–642. doi: 10.1016/j.euroneuro.2019.03.006

Choi, Y., Mericle, A., & Harachi, T. W. (2006). Using Rasch Analysis to Test the Cross-Cultural Item Equivalence of the Harvard Trauma Questionnaire and the Hopkins Symptom Checklist Across Vietnamese and Cambodian Immigrant Mothers. *Journal of Applied Measurement*, *7*(1), 16. Retrieved from /pmc/articles/PMC3292214/

Chong, T. T.-J., Bonnelle, V., Manohar, S., Veromann, K.-R., Muhammed, K., Tofaris, G. K., … Husain, M. (2015). Dopamine enhances willingness to exert effort for reward in Parkinson's disease. *Cortex*, *69*, 40–46. doi: 10.1016/j.cortex.2015.04.003

Chong, T. T.-J. T.-J., Apps, M., Giehl, K., Sillence, A., Grima, L. L., & Husain, M. (2017). Neurocomputational mechanisms underlying subjective valuation of effort costs. *PLOS Biology*, *15*(2), e1002598. doi: 10.1371/journal.pbio.1002598

Chong, T. T.-J. T. J., Bonnelle, V., & Husain, M. (2016). Quantifying motivation with effort-based decision-making paradigms in health and disease. In *Progress in Brain Research* (1st ed., Vol. 229, pp. 71–100). doi: 10.1016/bs.pbr.2016.05.002

Cléry-Melin, M.-L., Schmidt, L., Lafargue, G., Baup, N., Fossati, P., & Pessiglione, M. (2011). Why don't you try harder? An investigation of effort production in major depression. *PloS One*, *6*(8), e23178. doi: 10.1371/journal.pone.0023178

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences.* Academic Press.

Conroy, M. A., & Polich, J. (2007). Normative Variation of P3a and P3b from a Large Sample. *Journal of Psychophysiology*, *21*(1), 22–32. doi: 10.1027/0269-8803.21.1.22

Cooper, J. A., Barch, D. M., Reddy, L. F., Horan, W. P., Green, M. F., & Treadway, M. T. (2019). Effortful Goal-Directed Behavior in Schizophrenia: Computational Subtypes and Associations With Cognition. *Journal of Abnormal Psychology*, *128*(7), 710–722. doi: 10.1037/abn0000443

Cruz, A. F. (2019). *Brain mechanisms underlying cognitive dysfunction in HIV*. McGill University (Canada).

Culbreth, A. J., Moran, E. K., & Barch, D. M. (2018). Effort-cost decision-making in psychosis and depression: could a similar behavioral deficit arise from disparate psychological and neural mechanisms? *Psychological Medicine*, *48*(6), 889–904. doi: 10.1017/S0033291717002525

Cummings, J. L., Mega, M., Gray, K., Rosenberg-Thompson, S., Carusi, D. A., & Gornbein, J. (1994). The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, *44*(12), 2308.

Cysique, L. A., & Brew, B. J. (2019). Comorbid depression and apathy in HIV-associated neurocognitive disorders in the era of chronic HIV infection. In *Handbook of Clinical Neurology* (1st ed., Vol. 165, pp. 71–82). doi: 10.1016/B978-0-444-64012-3.00006-X

Dang, J., King, K. M., & Inzlicht, M. (2020). Why Are Self-Report and Behavioral Measures Weakly Correlated? *Trends in Cognitive Sciences*, *24*(4), 267–269. doi: 10.1016/j.tics.2020.01.007

Debruille, J. B., Touzel, M., Segal, J., Snidal, C., & Renoult, L. (2019). A Central Component of the N1 Event-Related Brain Potential Could Index the Early and Automatic Inhibition of the Actions Systematically Activated by Objects. *Frontiers in Behavioral Neuroscience*, *0*, 95. doi: 10.3389/FNBEH.2019.00095

Di Russo, F. (2003). Source Analysis of Event-related Cortical Activity during Visuo-spatial Attention. *Cerebral Cortex*, *13*(5), 486–499. doi: 10.1093/cercor/13.5.486

Dobryakova, E., Jessup, R. K., & Tricomi, E. (2017). Modulation of ventral striatal activity by cognitive effort. *Neuroimage*, *147*, 330–338. doi: https://dx.doi.org/10.1016/j.neuroimage.2016.12.029

Docx, L., de la Asuncion, J., Sabbe, B., Hoste, L., Baeten, R., Warnaerts, N., & Morrens, M. (2015). Effort discounting and its association with negative symptoms in schizophrenia. *Cogn Neuropsychiatry*, *20*(2), 172–185. doi: 10.1080/13546805.2014.993463

Draper, A., Koch, R. M., van der Meer, J. W., AJ Apps, M., Pickkers, P., Husain, M., & van der Schaaf, M. E. (2018). Effort but not Reward Sensitivity is Altered by Acute Sickness Induced by Experimental Endotoxemia in Humans. *Neuropsychopharmacology*, *43*(5), 1107–1118. doi: 10.1038/npp.2017.231

Eakman, A. M. (2012). Measurement Characteristics of the Engagement in Meaningful Activities

Survey in an Age-Diverse Sample. *The American Journal of Occupational Therapy*, *66*(2), e20. doi: 10.5014/AJOT.2012.001867

Eakman, A. M., Carlson, M. E., & Clark, F. A. (2010). The Meaningful Activity Participation Assessment: A Measure of Engagement in Personally Valued Activities: *Http://Dx.Doi.Org.Proxy3.Library.Mcgill.ca/10.2190/AG.70.4.B*, *70*(4), 299–317. doi: 10.2190/AG.70.4.B

Eggers, C., Arendt, G., Hahn, K., Husstedt, I. W., Maschke, M., Neuen-Jacob, E., … Straube, E. (2017). HIV-1-associated neurocognitive disorder: epidemiology, pathogenesis, diagnosis, and treatment. *Journal of Neurology*, *264*(8), 1715–1727. doi: 10.1007/s00415-017-8503-2

Ennis, G. E., Hess, T. M., & Smith, B. T. (2013). The impact of age and motivation on cognitive effort: Implications for cognitive engagement in older adulthood. *Psychology and Aging*, *28*(2), 495–504. doi: 10.1037/a0031255

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*(2), 175–191. doi: 10.3758/BF03193146

Fellows, L. K. (2004). The Cognitive Neuroscience of Human Decision Making: A Review and Conceptual Framework. *Behavioral and Cognitive Neuroscience Reviews*, *3*(3), 159–172. doi: 10.1177/1534582304273251

Fernandez Cruz, A. L., Chen, C.-M., Sanford, R., Collins, D. L., Brouillette, M.-J., Mayo, N. E., & Fellows, L. K. (2021). Multimodal neuroimaging markers of variation in cognitive ability in older HIV+ men. *PLOS ONE*, *16*(7), e0243670. doi: 10.1371/journal.pone.0243670

Fervaha, G., Duncan, M., Foussias, G., Agid, O., Faulkner, G. E., & Remington, G. (2015). Effort-based decision making as an objective paradigm for the assessment of motivational deficits in schizophrenia. *Schizophrenia Research*, *168*(1–2), 483–490. doi: 10.1016/j.schres.2015.07.023

Fervaha, G., Graff-Guerrero, A., Zakzanis, K. K., Foussias, G., Agid, O., & Remington, G. (2013). Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. *Journal of Psychiatric Research*, *47*(11), 1590–1596. doi: 10.1016/J.JPSYCHIRES.2013.08.003

Foti, D., Weinberg, A., Bernat, E. M., & Proudfit, G. H. (2015). Anterior cingulate activity to monetary loss and basal ganglia activity to monetary gain uniquely contribute to the feedback negativity. *Clinical Neurophysiology*, *126*(7), 1338–1347. doi: 10.1016/J.CLINPH.2014.08.025

Frey, B. S., & Jegen, R. (2001). Motivation Crowding Theory. *Journal of Economic Surveys*, *15*(5), 589–611. doi: 10.1111/1467-6419.00150

Gajewski, P. D., Ferdinand, N. K., Kray, J., & Falkenstein, M. (2018). Understanding sources of adult age differences in task switching: Evidence from behavioral and ERP studies. *Neuroscience & Biobehavioral Reviews*, *92*, 255–275. doi: 10.1016/J.NEUBIOREV.2018.05.029

Gehring, W. J. (2002). The Medial Frontal Cortex and the Rapid Processing of Monetary Gains and Losses. *Science*, *295*(5563), 2279–2282. doi: 10.1126/science.1066893

Glazer, J. E., Kelley, N. J., Pornpattananangkul, N., Mittal, V. A., & Nusslock, R. (2018). Beyond the FRN: Broadening the time-course of EEG and ERP components implicated in reward processing. *International Journal of Psychophysiology*, *132*, 184–202. doi: 10.1016/J.IJPSYCHO.2018.02.002

Glimcher, P. W., & Rustichini, A. (2004). Neuroeconomics: The consilience of brain and decision. *Science*, *306*(5695), 447–452. doi: 10.1126/science.1102566

Gold, J. M., Strauss, G. P., Waltz, J. A., Robinson, B. M., Brown, J. K., & Frank, M. J. (2013). Negative Symptoms of Schizophrenia Are Associated with Abnormal Effort-Cost Computations. *Biological Psychiatry*, *74*(2), 130–136. doi: 10.1016/j.biopsych.2012.12.022

González-Scarano, F., & Martín-García, J. (2005). The neuropathogenesis of AIDS. *Nature Reviews Immunology 2005 5:1*, *5*(1), 69–81. doi: 10.1038/nri1527

Goodwin, L. D., Leech, N. L., The, S., Education, E., Spring, N., Taylor, P., & Goodwin, L. D. (2016). *Understanding Correlation : Factors That Affect the Size of r Linked references are available on JSTOR for this article : Understanding Correlation : Factors That Affect the Size of r*. *74*(3), 251–266.

Greenson, R. R. (1949). The Psychology of Apathy. *Psychoanal. Q.*, *18*, 290–302.

Groeneweg-Koolhoven, I., Ploeg, M., Comijs, H. C., WJH Penninx, B., van der Mast, R. C.,

Schoevers, R. A., … Exel, E. van. (2017). Apathy in early and late-life depression. *Journal of Affective Disorders*, *223*, 76–81. doi: 10.1016/j.jad.2017.07.022

Hajcak, G., Holroyd, C. B., Moser, J. S., & Simons, R. F. (2005). Brain potentials associated with expected and unexpected good and bad outcomes. *Psychophysiology*, *42*(2), 161–170. doi: 10.1111/j.1469-8986.2005.00278.x

Hartmann, M. N., Hager, O. M., Reimann, A. V., Chumbley, J. R., Kirschner, M., Seifritz, E., … Kaiser, S. (2015). Apathy But Not Diminished Expression in Schizophrenia Is Associated With Discounting of Monetary Rewards by Physical Effort. *Schizophrenia Bulletin*, *41*(2), 503–512. doi: 10.1093/schbul/sbu102

Head, M. L., Holman, L., Lanfear, R., Kahn, A. T., & Jennions, M. D. (2015). The Extent and Consequences of P-Hacking in Science. *PLOS Biology*, *13*(3), e1002106. doi: 10.1371/JOURNAL.PBIO.1002106

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., … Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter Study. *Neurology*, *75*(23), 2087–2096. doi: 10.1212/WNL.0b013e318200d727

Hershenberg, R., Satterthwaite, T. D., Daldal, A., Katchmar, N., Moore, T. M., Kable, J. W., & Wolf, D. H. (2016). Diminished effort on a progressive ratio task in both unipolar and bipolar depression. *Journal of Affective Disorders*, *196*, 97–100. doi: 10.1016/j.jad.2016.02.003

Hess, T M, & Ennis, G. E. (2012). Age differences in the effort and costs associated with cognitive activity. *J Gerontol B Psychol Sci Soc Sci*, *67*(4), 447–455. doi: 10.1093/geronb/gbr129

Hess, T M, & Ennis, G. E. (2014). Assessment of Adult Age differences in Task Engagement: The Utility of Systolic Blood Pressure. *Motiv Emot*, *38*(6), 844–854. doi: 10.1007/s11031-014-9433-2

Hess, Thomas M., Smith, B. T., & Sharifian, N. (2016). Aging and effort expenditure: The impact of subjective perceptions of task demands. *Psychology and Aging*, *31*(7), 653–660. doi: 10.1037/pag0000127

Hoare, J., Jean-Paul Fouche, Fcp., Bruce Spottiswoode, H., Joska, J. A., Renata Schoeman, Fcp.,

Dan Stein, Mm. J., … Carey, P. D. (2010). White Matter Correlates of Apathy in HIV-Positive Subjects: A Diffusion Tensor Imaging Study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *22*(3), 313–320. doi: 10.1176/appi.neuropsych.22.3.313

Holroyd, C. B., & Krigolson, O. E. (2007). Reward prediction error signals associated with a modified time estimation task. *Psychophysiology*, *44*(6), 913–917. doi: 10.1111/j.1469-8986.2007.00561.x

Holroyd, C. B., Krigolson, O. E., & Lee, S. (2011). Reward positivity elicited by predictive cues. *NeuroReport*, *22*(5), 249–252. doi: 10.1097/WNR.0B013E328345441D

Holroyd, C. B., Larsen, J. T., & Cohen, J. D. (2004). Context dependence of the event-related brain potential associated with reward and punishment. *Psychophysiology*, *41*(2), 245–253. doi: 10.1111/j.1469-8986.2004.00152.x

Hölttä, E. H., Laakkonen, M.-L., Laurila, J. V., Strandberg, T. E., Tilvis, R. S., & Pitkälä, K. H. (2012). Apathy: Prevalence, Associated Factors, and Prognostic Value Among Frail, Older Inpatients. *Journal of the American Medical Directors Association*, *13*(6), 541–545. doi: 10.1016/j.jamda.2012.04.005

Hooker, S. A., Masters, K. S., Vagnini, K. M., & Rush, C. L. (2020a). Engaging in personally meaningful activities is associated with meaning salience and psychological well-being. *Journal of Positive Psychology*, *15*(6), 821–831. doi: 10.1080/17439760.2019.1651895

Hooker, S. A., Masters, K. S., Vagnini, K. M., & Rush, C. L. (2020b). Engaging in personally meaningful activities is associated with meaning salience and psychological well-being. *Journal of Positive Psychology*, *15*(6), 821–831. doi: 10.1080/17439760.2019.1651895

Horan, W. P., Reddy, L. F., Barch, D. M., Buchanan, R. W., Dunayevich, E., Gold, J. M., … Green, M. F. (2015). Effort-Based Decision-Making Paradigms for Clinical Trials in Schizophrenia: Part 2—External Validity and Correlates. *Schizophrenia Bulletin*, *41*(5), 1055–1065. doi: 10.1093/schbul/sbv090

Huang, J., Yang, X., Lan, Y., Zhu, C., Liu, X., Wang, Y., … Chan, R. C. K. (2016). Neural substrates of the impaired effort expenditure decision making in schizophrenia. *Neuropsychology*, *30*(6), 685–696. doi: 10.1037/neu0000284

Hughes, D. M., Yates, M. J., Morton, E. E., & Smillie, L. D. (2015). Asymmetric frontal cortical

activity predicts effort expenditure for reward. *Social Cognitive and Affective Neuroscience*, *10*(7), 1015–1019. doi: 10.1093/scan/nsu149

Hum, S., Fellows, L. K., Lourenco, C., & Mayo, N. E. (2021). Are the Items of the Starkstein Apathy Scale Fit for the Purpose of Measuring Apathy Post-Stroke? *MedRxiv*, 2021.05.05.21256484. doi: https://doi.org/10.1101/2021.05.05.21256484

Husain, M., & Roiser, J. P. (2018). Neuroscience of apathy and anhedonia: a transdiagnostic approach. *Nature Reviews Neuroscience*, *19*(8), 470–484. doi: 10.1038/s41583-018-0029-9

Johansson, M., Stomrud, E., Lindberg, O., Westman, E., Johansson, P. M., van Westen, D., … Hansson, O. (2020). Apathy and anxiety are early markers of Alzheimer's disease. *Neurobiology of Aging*, *85*, 74–82. doi: 10.1016/j.neurobiolaging.2019.10.008

Kamat, R., Brown, G. G., Bolden, K., Fennema-Notestein, C., Archibald, S., Marcotte, T. D., … Heaton, R. K. (2014). Apathy is associated with white matter abnormalities in anterior, medial brain regions in persons with HIV infection. *Journal of Clinical and Experimental Neuropsychology*, *36*(8), 854–866. doi: 10.1080/13803395.2014.950636

Kamat, R., Woods, S. P., Cameron, M. V, Iudicello, J. E., & HIV Neurobehavioral Research Program (HNRP) Group, T. H. N. R. P. (HNRP). (2016). Apathy is associated with lower mental and physical quality of life in persons infected with HIV. *Psychology, Health & Medicine*, *21*(7), 890–901. doi: 10.1080/13548506.2015.1131998

Kamat, R., Woods, S. P., Marcotte, T. D., Ellis, R. J., Grant, I., & HIV Neurobehavioral Research Program (HNRP) Group. (2012). Implications of apathy for everyday functioning outcomes in persons living with HIV infection. *Archives of Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists*, *27*(5), 520–531. doi: 10.1093/arclin/acs055

Kaur, N., Dendukuri, N., Fellows, L. K., Brouillette, M. J., & Mayo, N. (2019). Association between cognitive reserve and cognitive performance in people with HIV: a systematic review and meta-analysis. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV*, *0121*(May 2019). doi: 10.1080/09540121.2019.1612017

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.

Kleih, S.C., Nijboer, F., Halder, S., & Kübler, A. (2010). Motivation modulates the P300 amplitude during brain–computer interface use. *Clinical Neurophysiology*, *121*(7), 1023–1031. doi: 10.1016/j.clinph.2010.01.034

Kleih, Sonja C., & Kubler, A. (2013). Empathy, motivation, and p300-BCI performance. *Frontiers in Human Neuroscience*, *7*(OCT). doi: 10.3389/fnhum.2013.00642

Klimas, N., Koneru, A. O. B., & Fletcher, M. A. (2008). Overview of HIV. *Psychosomatic Medicine*, *70*(5), 523–530. doi: 10.1097/PSY.0b013e31817ae69f

Klostermann, E. C., Braskie, M. N., Landau, S. M., O'Neil, J. P., & Jagust, W. J. (2012). Dopamine and frontostriatal networks in cognitive aging. *Neurobiology of Aging*, *33*(3), 623.e15-623.e24. doi: 10.1016/J.NEUROBIOLAGING.2011.03.002

Kramer-Hämmerle, S., Rothenaigner, I., Wolff, H., Bell, J. E., & Brack-Werner, R. (2005). Cells of the central nervous system as targets and reservoirs of the human immunodeficiency virus. *Virus Research*, *111*(2), 194–213. doi: 10.1016/J.VIRUSRES.2005.04.009

Kurniawan, I. T., Seymour, B., Talmi, D., Yoshida, W., Chater, N., & Dolan, R. J. (2010). Choosing to Make an Effort: The Role of Striatum in Signaling Physical Effort of a Chosen Action. *Journal of Neurophysiology*, *104*(1), 313–321. doi: 10.1152/jn.00027.2010

Lacourt, T. E., Vichaya, E. G., Escalante, C., Manzullo, E. F., Gunn, B., Hess, K. R., … Dantzer, R. (2018). An effort expenditure perspective on cancer-related fatigue. *Psychoneuroendocrinology*, *96*(June), 109–117. doi: 10.1016/j.psyneuen.2018.06.009

Lam, A., Mayo, N. E., Scott, S., Brouillette, M. J., & Fellows, L. K. (2019). HIV-Related stigma affects cognition in older men living with HIV. *Journal of Acquired Immune Deficiency Syndromes*, *80*(2), 198–204. doi: 10.1097/QAI.0000000000001898

Lasselin, J., Treadway, M. T., Lacourt, T. E., Soop, A., Olsson, M. J., Karshikoff, B., … Lekander, M. (2017). Lipopolysaccharide Alters Motivated Behavior in a Monetary Reward Task: A Randomized Trial. *Neuropsychopharmacology*, *42*(4), 801–810. doi: 10.1038/npp.2016.191

Lavretsky, H., Ballmaier, M., Pham, D., Toga, A., & Kumar, A. (2007). Neuroanatomical Characteristics of Geriatric Apathy and Depression: A Magnetic Resonance Imaging Study. *The American Journal of Geriatric Psychiatry*, *15*(5), 386–394. doi: 10.1097/JGP.0B013E3180325A16

Lawrence, A. D., Goerendt, I. K., & Brooks, D. J. (2011). Apathy blunts neural response to money in Parkinson's disease. *Social Neuroscience*, *6*(5–6), 653–662. doi: 10.1080/17470919.2011.556821

Le Bouc, R., Rigoux, L., Schmidt, L., Degos, B., Welter, M., Vidailhet, M., … Pessiglione, M. (2016). Computational Dissection of Dopamine Motor and Motivational Functions in Humans. *The Journal of Neuroscience*, *36*(25), 6623–6633. doi: 10.1523/JNEUROSCI.3078-15.2016

Le Heron, C., Holroyd, C. B., Salamone, J., Husain, M., & Heron, L. (2018). Brain mechanisms underlying apathy. *J Neurol Neurosurg Psychiatry*, *0*, jnnp-2018-318265. doi: 10.1136/jnnp-2018-318265

Le Heron, C., Manohar, S., Plant, O., Muhammed, K., Griffanti, L., Nemeth, A., … Husain, M. (2018). Dysfunctional effort-based decision-making underlies apathy in genetic cerebral small vessel disease. *Brain*, *141*(11), 3193–3210. doi: 10.1093/brain/awy257

Le Heron, C., Plant, O., Manohar, S., Ang, Y.-S., Jackson, M., Lennox, G., … Husain, M. (2018). Distinct effects of apathy and dopamine on effort-based decision-making in Parkinson's disease. *Brain*, *141*(5), 1455–1469. doi: 10.1093/brain/awy110

Lee, W., & Reeve, J. (2017). Identifying the neural substrates of intrinsic motivation during task performance. *Cognitive, Affective and Behavioral Neuroscience*, *17*(5), 939–953. doi: 10.3758/s13415-017-0524-x

Levy, M. L., Cummings, J. L., Fairbanks, L. A., Masterman, D., Miller, B. L., Craig, A. H., … Litvan, I. (1998). Apathy Is Not Depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *10*(3), 314–319. doi: 10.1176/jnp.10.3.314

Levy, R., & Dubois, B. (2006). Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits. *Cerebral Cortex*, *16*(7), 916–928. doi: 10.1093/cercor/bhj043

Lourenço, C. B. (2014). *Apathy in Stroke : Conceptualization , Measurement , and Impact degree of the Doctor in Philosophy*. McGill.

Luck, S. J., Woodman, G. F., & Vogel, E. K. (2000). Event-related potential studies of attention. *Trends in Cognitive Sciences*, *4*(11), 432–440. doi: 10.1016/S1364-6613(00)01545-X

Luu, P., & Ferree, T. (2005). Determination of the HydroCel Geodesic Sensor Nets' average

electrode positions and their 10–10 international equivalents. *Inc, Technical Note*, 1–11.

Mann, R. S. (1990). *Differential Diagnosis and Classification of Apathy*. Retrieved from http://ajp.psychiatryonline.org.proxy3.library.mcgill.ca/doi/pdf/10.1176/ajp.147.1.22

Marin, R. S., Biedrzycki, R. C., & Firinciogullari, S. (1991). Reliability and validity of the apathy evaluation scale. *Psychiatry Research*, *38*(2), 143–162. doi: 10.1016/0165-1781(91)90040-V

Marin, R. S., & Wilkosz, P. A. (2005a). *Disorders of diminished motivation*. *20*(4), 377–388.

Marin, R. S., & Wilkosz, P. A. (2005b). *Motivation*. *20*(4), 377–388.

Martinez-Horta, S., Riba, J., de Bobadilla, R. F., Pagonabarraga, J., Pascual-Sedano, B., Antonijoan, R. M., … Kulisevsky, J. (2014). Apathy in Parkinson's Disease: Neurophysiological Evidence of Impaired Incentive Processing. *Journal of Neuroscience*, *34*(17), 5918–5926. doi: 10.1523/JNEUROSCI.0251-14.2014

Mathis, S., Neau, J.-P., Pluchon, C., Fargeau, M.-N., Karolewicz, S., Iljicsov, A., & Gil, R. (2014). Apathy in Parkinson's Disease: An Electrophysiological Study. *Neurology Research International*, *2014*, 1–9. doi: 10.1155/2014/290513

Mayo, N. E., Brouillette, M.-J., & Fellows, L. K. (2018). Estimates of Prevalence of Cognitive Impairment From Research Studies Can Be Affected by Selection Bias. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *78*(2), e7–e8. doi: 10.1097/QAI.0000000000001668

Mayo, N. E., Brouillette, M.-J., Fellows, L. K., & Investigators, P. B. H. N. (2016). Understanding and optimizing brain health in HIV now: protocol for a longitudinal cohort study with multiple randomized controlled trials. *BMC Neurology*, *16*(8). doi: 10.1186/s12883-016-0527-1

Mayo, N. E., Brouillette, M.-J., Scott, S. C., Harris, M., Smaill, F., Smith, G., … Fellows, L. K. (2020). Relationships between cognition, function, and quality of life among HIV+ Canadian men. *Quality of Life Research*, *29*(1), 37–55. doi: 10.1007/s11136-019-02291-w

McCarthy, J. M., Treadway, M. T., Bennett, M. E., & Blanchard, J. J. (2016). Inefficient effort allocation and negative symptoms in individuals with schizophrenia. *Schizophrenia Research*, *170*(2–3), 278–284. doi: 10.1016/j.schres.2015.12.017

Mccusker, M. (2015). Apathy: Who Cares? A Concept Analysis. *Issues in Mental Health Nursing*,

36(9), 693–697. doi: 10.3109/01612840.2015.1022844

McIntosh, R. C., Rosselli, M., Uddin, L. Q., & Antoni, M. (2015). Neuropathological sequelae of Human Immunodeficiency Virus and apathy: A review of neuropsychological and neuroimaging studies. *Neuroscience & Biobehavioral Reviews*, *55*, 147–164. doi: 10.1016/j.neubiorev.2015.04.008

Merchant, R. A., Morley, J. E., & Izquierdo, M. (2021). Exercise, Aging and Frailty: Guidelines for Increasing Function. *The Journal of Nutrition, Health & Aging 2021 25:4*, *25*(4), 405–409. doi: 10.1007/S12603-021-1590-X

Millana, M., Fone, K., Steckler, T., & Horan, W. (2014). Negative symptoms of schizophrenia: Clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *Neuropsychopharmacology*, *24*, 645–692.

Miller, D. S., Robert, P., Ereshefsky, L., Adler, L., Bateman, D., Cummings, J., … Lanctôt, K. L. (2021). Diagnostic criteria for apathy in neurocognitive disorders. *Alzheimer's & Dementia*. doi: 10.1002/ALZ.12358

Miltner, W. H. R. R., Braun, C. H., & Coles, M. G. H. H. (1997). Event-Related Brain Potentials Following Incorrect Feedback in a Time-Estimation Task: Evidence for a "Generic" Neural System for Error Detection. *Journal of Cognitive Neuroscience*, *9*(6), 788–798. doi: 10.1162/jocn.1997.9.6.788

Montoya-Murillo, G., Ibarretxe-Bilbao, N., Peña, J., & Ojeda, N. (2019). The impact of apathy on cognitive performance in the elderly. *International Journal of Geriatric Psychiatry*, *34*(5), 657–665. doi: 10.1002/gps.5062

Murayama, K., Matsumoto, M., Izuma, K., & Matsumoto, K. (2010). Neural basis of the undermining effect of monetary reward on intrinsic motivation. *Proceedings of the National Academy of Sciences*, *107*(49), 20911–20916. doi: 10.1073/pnas.1013305107

Nasreddine, Z. S., Phillips, N. A., BÃ©dirian, V., Charbonneau, S., Whitehead, V., Collin, I., … Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Nevid, J. S. (2012). *Psychology: Concepts and applications*. Cengage Learning.

Nobis, L. (2018). Apathy in Alzheimer's disease. *Current Opinion in Behavioral Sciences*, *22*, 7–13. doi: 10.1016/J.COBEHA.2017.12.007

O'Connor, E., & Zeffiro, T. (2019). Is treated HIV infection still toxic to the brain? *Progress in Molecular Biology and Translational Science*, *165*, 259–284. doi: 10.1016/BS.PMBTS.2019.04.001

Palidis, D. J., Cashaback, J. G. A., & Gribble, P. L. (2019). Neural signatures of reward and sensory error feedback processing in motor learning. *Journal of Neurophysiology*, *121*(4), 1561–1574. doi: 10.1152/jn.00792.2018

Pallant, J. F., & Tennant, A. (2007, March 1). An introduction to the Rasch measurement model: An example using the Hospital Anxiety and Depression Scale (HADS). *British Journal of Clinical Psychology*, Vol. 46, pp. 1–18. doi: 10.1348/014466506X96931

Paul, R., Flanigan, T. P., Tashima, K., Cohen, R., Lawrence, J., Alt, E., … Hinkin, C. (2005). Apathy correlates with cognitive function but not CD4 status in patients with Human Immunodeficiency Virus. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(1), 114–118. doi: 10.1176/jnp.17.1.114

Paul, R. H., Brickman, A. M., Navia, B., Hinkin, C., Malloy, P. F., Jefferson, A. L., … Flanigan, T. P. (2005). Apathy is Associated With Volume of the Nucleus Accumbens in Patients Infected With HIV. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(2), 167–171. doi: 10.1176/jnp.17.2.167

Pedersen, K. F., Alves, G., Larsen, J. P., Tysnes, O.-B., Møller, S. G., & Brønnick, K. (2012). Psychometric Properties of the Starkstein Apathy Scale in Patients With Early Untreated Parkinson Disease. *The American Journal of Geriatric Psychiatry*, *20*(2), 142–148. doi: 10.1097/JGP.0b013e31823038f2

Pessiglione, M., Vinckier, F., Bouret, S., Daunizeau, J., & Le Bouc, R. (2018). Why not try harder? Computational approach to motivation deficits in neuro-psychiatric diseases. *Brain*, *141*(3), 629–650. doi: 10.1093/brain/awx278

Peterburs, J., Suchan, B., & Bellebaum, C. (2013). You do the math: coding of bets and outcomes in a gambling task in the feedback-related negativity and p300 in healthy adults. *PloS One*, *8*(11), e81262. doi: 10.1371/journal.pone.0081262

Pimontel, M. A., Kanellopoulos, D., & Gunning, F. M. (2020). Neuroanatomical Abnormalities in Older Depressed Adults With Apathy: A Systematic Review. *Journal of Geriatric Psychiatry and Neurology*, *33*(5), 289–303. doi: 10.1177/0891988719882100

Plessis, S. Du, Vink, M., Joska, J. A., Koutsilieri, E., Stein, D. J., & Emsley, R. (2014). HIV infection and the fronto–striatal system. *AIDS*, *28*(6), 803–811. doi: 10.1097/QAD.0000000000000151

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology*, *118*(10), 2128–2148. doi: 10.1016/j.clinph.2007.04.019

Porat, O., Hassin-Baer, S., Cohen, O. S., Markus, A., & Tomer, R. (2014). Asymmetric dopamine loss differentially affects effort to maximize gain or minimize loss. *Cortex*, *51*, 82–91. doi: 10.1016/j.cortex.2013.10.004

Proudfit, G. H. (2015). The reward positivity: From basic research on reward to a biomarker for depression. *Psychophysiology*, *52*(4), 449–459. doi: 10.1111/psyp.12370

Proudfit, G. H., Bress, J. N., Foti, D., Kujawa, A., & Klein, D. N. (2015). Depression and event-related potentials: emotional disengagement and reward insensitivity. *Current Opinion in Psychology*, *4*, 110–113. doi: 10.1016/J.COPSYC.2014.12.018

Public Health Agency of Canada. (2020). *People living with HIV in Canada: infographic*. Retrieved from https://www.canada.ca/en/public-health/services/publications/diseases-conditions/hiv-canada.html

Reddy, L. F., Horan, W. P., Barch, D. M., Buchanan, R. W., Dunayevich, E., Gold, J. M., … Green, M. F. (2015). Effort-Based Decision-Making Paradigms for Clinical Trials in Schizophrenia: Part 1—Psychometric Characteristics of 5 Paradigms. *Schizophrenia Bulletin*, *41*(5), 1045–1054. doi: 10.1093/schbul/sbv089

Reekum, R. van, Stuss, D. T., & Ostrander, L. (2005). Apathy: why care?. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *17*(1), 7–19. Retrieved from http://neuro.psychiatryonline.org/doi/pdf/10.1176/jnp.17.1.7

Robert, P., Lanctôt, K. L., Agüera-Ortiz, L., Aalten, P., Bremond, F., Defrancesco, M., … Manera, V. (2018). Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group. *European Psychiatry*, *54*, 71–76. doi:

10.1016/j.eurpsy.2018.07.008

Rossini, P. M., Rossi, S., Babiloni, C., & Polich, J. (2007). Clinical neurophysiology of aging brain: From normal aging to neurodegeneration. *Progress in Neurobiology*, *83*(6), 375–400. doi: 10.1016/J.PNEUROBIO.2007.07.010

Roy, E. P., Riggs, J. E., Martin, M., Ringel, M., & Gutmann, L. (1988). *Familial parkinsonism, apathy, weight, loss, and central hypoventilation:Succesful long-term management*. (April), 637–639.

Rubin, L. H., & Maki, P. M. (2019). HIV, Depression, and Cognitive Impairment in the Era of Effective Antiretroviral Therapy. *Current HIV/AIDS Reports*, *16*(1), 82–95. doi: 10.1007/s11904-019-00421-0

Russo, F. Di, Martínez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. A. (2002). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping*, *15*(2), 95–111. doi: 10.1002/HBM.10010

Ryan, R. M., & Deci, E. L. (1985). *Self-Determination Theory and the Facilitation of Intrinsic Motivation, Social Development, and Well-Being Self-Determination Theory*. Retrieved from Ryan website: https://selfdeterminationtheory.org/SDT/documents/2000_RyanDeci_SDT.pdf

Salamone, J. D., Correa, M., Farrar, A., & Mingote, S. M. (2007). Effort-related functions of nucleus accumbens dopamine and associated forebrain circuits. *Psychopharmacology*, *191*(3), 461–482. doi: https://dx.doi.org/10.1007/s00213-006-0668-9

Salamone, John D, Yohn, S. E., López-Cruz, L., San Miguel, N., & Correa, M. (2016). Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology. *Brain*, *139*(5), 1325–1347. doi: 10.1093/brain/aww050

Samanez-Larkin, G. R., & Knutson, B. (2015). Decision making in the ageing brain: changes in affective and motivational circuits. *Nature Reviews. Neuroscience*, *16*(5), 278–289. doi: 10.1038/nrn3917

San Francisco, CA: University of California, S. F. I. for H. & A. (2003). *Community Healthy Activities Model Program for Seniors II (CHAMPS II): Program Manual.*

San Martín, R. (2012). Event-related potential studies of outcome processing and feedback-

guided learning. *Frontiers in Human Neuroscience*, *6*(November), 304. doi: 10.3389/fnhum.2012.00304

Sandra, D. A., & Otto, A. R. (2018). Cognitive capacity limitations and Need for Cognition differentially predict reward-induced cognitive effort expenditure. *Cognition*, *172*(December 2017), 101–106. doi: 10.1016/j.cognition.2017.12.004

Sanford, R., Ances, B. M., Meyerhoff, D. J., Price, R. W., Fuchs, D., Zetterberg, H., … Louis Collins, D. (2018). Longitudinal Trajectories of Brain Volume and Cortical Thickness in Treated and Untreated Primary Human Immunodeficiency Virus Infection. *Clinical Infectious Diseases*, *67*(11), 1705–1711. doi: 10.1093/cid/ciy362

Sanford, R., Cruz, A. L. F., Scott, S. C., Mayo, N. E., Fellows, L. K., Ances, B. M., & Collins, D. L. (2017). Regionally specific brain volumetric and cortical thickness changes in HIV-infected patients in the HAART era. *Journal of Acquired Immune Deficiency Syndromes*, *74*(5), 563–570. doi: 10.1097/QAI.0000000000001294

Sanford, R., Fellows, L. K., Ances, B. M., & Collins, D. L. (2018). Association of Brain Structure Changes and Cognitive Function With Combination Antiretroviral Therapy in HIV-Positive Individuals. *JAMA Neurology*, *75*(1), 72. doi: 10.1001/jamaneurol.2017.3036

Sato, A., Yasuda, A., Ohira, H., Miyawaki, K., Nishikawa, M., Kumano, H., & Kuboki, T. (2005). Effects of value and reward magnitude on feedback negativity and P300. *NeuroReport*, *16*(4), 407–411. doi: 10.1097/00001756-200503150-00020

Schaefer, H., & Martin, P. (1966). Behavioral therapy for apathy of hospitalized schizophrenics. *Psychological Reports*, 1147–1158. Retrieved from http://psychiatryonline.org/doi/abs/10.1176/jnp.10.3.314

Semprini, R., Lubrano, A., Misaggi, G., & Martorana, A. (2012). Apathy as marker of frail status. *Journal of Aging Research*, *2012*, 436251.

Simon, J. J., Biller, A., Walther, S., Roesch-Ely, D., Stippich, C., Weisbrod, M., & Kaiser, S. (2010). Neural correlates of reward processing in schizophrenia — Relationship to apathy and depression. *Schizophrenia Research*, *118*(1–3), 154–161. doi: 10.1016/J.SCHRES.2009.11.007

Simpson, E. H., & Balsam, P. D. (2015). The Behavioral Neuroscience of Motivation: An

Overview of Concepts, Measures, and Translational Applications. In *Current Topics in Behavioral Neurosciences* (Vol. 27, pp. 1–12). doi: 10.1007/7854_2015_402

Sims, A. (2003). Symptoms in the mind: An introduction to descriptive psychopathology. London: WB Saunders. *Marrero, M*.

Smith, R. M. (2004). *Introduction to Rasch measurement: Theory, models and applications*. Jam Press.

Sockeel, P., Dujardin, K., Sockeel, P., Devos, D., Denève, C., Destée, A., & Defebvre, L. (2006). The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *77*(5), 579–584. doi: 10.1136/jnnp.2005.075929

Spyrou, L., & Sanei, S. (2008). Source localization of event-related potentials incorporating spatial notch filters. *IEEE Transactions on Biomedical Engineering*, *55*(9), 2232–2239. doi: 10.1109/TBME.2008.920872

Starkstein, S. . E., & Leentjens, A. F. G. (2008). The nosological position of apathy in clinical practice. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(10), 1088–1092. doi: 10.1136/jnnp.2007.136895

Starkstein, S. ., Mayberg, H. ., Preziosi, T., Andrezejewski, P., Leiguarda, R., & Robinson, R. G. (1992). Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *4*(2), 134–139. doi: 10.1176/jnp.4.2.134

Starkstein, S. E., Fedoroff, J. P., Price, T. R., Leiguarda, R., & Robinson, R. G. (1993). Apathy following cerebrovascular lesions. *Stroke*, *24*(11), 1625–1630. doi: 10.1161/01.STR.24.11.1625

Stewart, A. L., Mills, K. M., King, A. C., Haskell, W. L., Gillis, D., & Ritter, P. L. (2001). CHAMPS physical activity questionnaire for older adults: Outcomes for interventions. *Medicine and Science in Sports and Exercise*, *33*(7), 1126–1141. doi: 10.1097/00005768-200107000-00010

Strombach, T., Strang, S., Park, S. Q., & Kenning, P. (2016). Common and distinctive approaches to motivation in different disciplines. In *Progress in Brain Research* (1st ed., Vol. 229). doi:

10.1016/bs.pbr.2016.06.007

Studer, B., & Knecht, S. (2016). A benefit–cost framework of motivation for a specific activity. In *Progress in Brain Research* (1st ed., Vol. 229). doi: 10.1016/bs.pbr.2016.06.014

Subramaniapillai, M., Mansur, R. B., Zuckerman, H., Park, C., Lee, Y., Iacobucci, M., … McIntyre, R. S. (2019). Association between cognitive function and performance on effort based decision making in patients with major depressive disorder treated with Vortioxetine. *Comprehensive Psychiatry*, *94*, 152113. doi: 10.1016/j.comppsych.2019.07.006

Tadel, F., Baillet, S., Mosher, J. C., Pantazis, D., & Leahy, R. M. (2011). Brainstorm: A User-Friendly Application for MEG/EEG Analysis. *Computational Intelligence and Neuroscience*, *2011*, 1–13. doi: 10.1155/2011/879716

Takayoshi, H., Onoda, K., & Yamaguchi, S. (2018). Do Event-Related Evoked Potentials Reflect Apathy Tendency and Motivation? *Frontiers in Human Neuroscience*, *12*(January), 1–10. doi: 10.3389/fnhum.2018.00011

Takeda, K., Matsumoto, M., Ogata, Y., Maida, K., Murakami, H., Murayama, K., … Nakagome, K. (2017). Impaired prefrontal activity to regulate the intrinsic motivation-action link in schizophrenia. *NeuroImage. Clinical*, *16*, 32–42. doi: 10.1016/j.nicl.2017.07.003

Tan, S. H., & Tan, S. B. (2010). The Correct Interpretation of Confidence Intervals. *Proceedings of Singapore Healthcare*, *19*(3), 276–278. doi: 10.1177/201010581001900316

Treadway, M. T., Bossaller, N. A., Shelton, R. C., & Zald, D. H. (2012). Effort-based decision-making in major depressive disorder: A translational model of motivational anhedonia. *Journal of Abnormal Psychology*, *121*(3), 553–558. doi: 10.1037/a0028813

Treadway, M. T., Buckholtz, J. W., Cowan, R. L., Woodward, N. D., Li, R., Ansari, M. S., … Zald, D. H. (2012). Dopaminergic Mechanisms of Individual Differences in Human Effort-Based Decision-Making. *Journal of Neuroscience*, *32*(18), 6170–6176. doi: https://dx.doi.org/10.1523/JNEUROSCI.6459-11.2012

Treadway, M. T., Buckholtz, J. W., Schwartzman, A. N., Lambert, W. E., & Zald, D. H. (2009). Worth the "EEfRT"? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PloS One*, *4*(8), e6598. doi: 10.1371/journal.pone.0006598

Treadway, M. T., Peterman, J. S., Zald, D. H., & Park, S. (2015). Impaired effort allocation in

patients with schizophrenia. *Schizophrenia Research*, *161*(2–3), 382–385. doi: https://dx.doi.org/10.1016/j.schres.2014.11.024

van Sighem, A., Gras, L., Reiss, P., Brinkman, K., & de Wolf, F. (2010). Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *Aids*, *24*(10), 1527–1535. doi: 10.1097/QAD.0b013e32833a3946

Wardle, M. C., Treadway, M. T., Mayo, L. M., Zald, D. H., & de Wit, H. (2011). Amping Up Effort: Effects of d-Amphetamine on Human Effort-Based Decision-Making. *Journal of Neuroscience*, *31*(46), 16597–16602. doi: 10.1523/JNEUROSCI.4387-11.2011

Willem van Dalen, J., van Wanrooij, L. L., Moll van Charante, E. P., Brayne, C., van Gool, W. A., & Richard, E. (2018). Association of Apathy With Risk of Incident Dementia. *JAMA Psychiatry*. doi: 10.1001/jamapsychiatry.2018.1877

Yamagata, S., Yamaguchi, S., & Kobayashi, S. (2004). Impaired Novelty Processing in Apathy After Subcortical Stroke. *Stroke*, *35*(8), 1935–1940. doi: 10.1161/01.STR.0000135017.51144.c9

Yang, X., Huang, J., Harrision, P., Roser, M. E., Tian, K., Wang, D., & Liu, G. (2021). Motivational differences in unipolar and bipolar depression, manic bipolar, acute and stable phase schizophrenia. *Journal of Affective Disorders*, *283*(February), 254–261. doi: 10.1016/j.jad.2021.01.075

Yao, H., Takashima, Y., Mori, T., Uchino, A., Hashimoto, M., Yuzuriha, T., … Sasaguri, T. (2009). Hypertension and white matter lesions are independently associated with apathetic behavior in healthy elderly subjects: the Sefuri brain MRI study. *Hypertension Research 2009 32:7*, *32*(7), 586–590. doi: 10.1038/hr.2009.65

Zénon, A., Duclos, Y., Carron, R., Witjas, T., Baunez, C., Régis, J., … Eusebio, A. (2016). The human subthalamic nucleus encodes the subjective value of reward and the cost of effort during decision-making. *Brain*, *139*(6), 1830–1843. doi: 10.1093/brain/aww075

Zhu, J., & Paul, W. E. (2008). CD4 T cells: fates, functions, and faults. *Blood*, *112*(5), 1557–1569. doi: 10.1182/BLOOD-2008-05-078154

Zigmond, A. S., & Snaith, R. P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatrica Scandinavica*, *67*(6), 361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x