The Acute Effects of A Single Dose (10 mg) of Selegiline on Emotional and Reward Processing in Healthy Volunteers

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aileme...

"Naming suffering, exalting it, dissecting it into its smallest components – that is doubtless a way to curb mourning."

Julia Kristeva

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ii. Declaration

The data analysed as part of this MSc by Research project was collected by me. I declare that all analyses reported in this thesis were performed by myself and that the write-up does not exceed the maximum word limit set for the MSc by Research thesis.

iii. Abbreviations:

PD: Parkinson's Disease
DSM-5: The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
VTA: Ventral Tegmental Area
NAc: Nucleus Accumbens
MAO: Monoamine Oxidase
MAO-I: Monoamine Oxidase Inhibitor
MDD: Major Depressive Disorder
RPE: Reward Prediction Error
SSRI: Selective Serotonin Reuptake Inhibitor
PET: Positron Emission Tomography
ELA: Early Life Adversity
fMRI: Functional Magnetic Resonance Imaging
CBT: Cognitive Behavioural Therapy
BAT: Behavioural Activation Therapy
DAT: Dopamine Transporter
SCID: Structured Clinical Interview for DSM-IV
BDI: Beck Depression Inventory
PANAS: Positive and Negative Affect Schedule
NART: National Adult Reading Test
EPQ: Eysenck Personality Questionnaire
STAI-T: State-Trait Anxiety Inventory - Trait
STAI-S: State-Trait Anxiety Inventory - State
SHAPS: Snaith-Hamilton Pleasure Scale
TEPS: Temporal Experience of Pleasure Scale
BMI: Body Mass Index

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PART I:

Research Background

Justifying An Alternative Approach to Depression Therapeutics

An Introductory Exposition:

Depression is one of the leading disabilities worldwide. However, existing treatment approaches remain ineffective for one-third of depressed patients. (Al-Harbi, 2012) Clinical findings and neuropsychological research corroborate that there is an overlap between poor treatment outcomes and dysfunction in reward processing, which presents as *anhedonia*, "the loss of interest and/or pleasure." (Rizvi et al., 2016) As a result, research that aims to find alternative treatment approaches to depression has been inspired to address the neuropsychological construct of 'reward' specifically by examining a well-established 'reward' molecule: dopamine.

Interestingly, Parkinson's Disease, a neurological disorder, is caused by the apoptosis of dopamine-producing neurons in the substantia nigra. Hence, the pharmacological interventions used in treating Parkinson's Disease have the potential to address this particular gap relating to reward processing in treatment-resistant depression.

One such Parkinson's Disease medication, selegiline, is known for its tolerable side-effect profile and dopamine-specific pharmacological mechanism.

Several methods are employed to evaluate the effectiveness of a prospective pharmaceutical as an antidepressant. While most can establish a direct correlation between successful treatments and their impact on depressive symptoms, the precise connection between neurobiological effects and ensuing psychological changes remains elusive. To bridge this gap, behavioural tasks conducted during acute medication treatment have proven instrumental in shedding light on this intricate relationship. (Godlewska and Harmer, 2021)

The following chapters will present a case for assessing selegiline's efficacy as an antidepressant using this framework. Through this exploration, we aim to enhance our understanding of the neuropsychological mechanisms influenced by selegiline in the treatment of depression. This, in turn, will enable us to target specific subtypes more effectively.

Chapter I: There is Something Weird About Moods

When distinguishing depression or other psychiatric illnesses from a 'healthy' state, a fundamental question arises: when do symptoms cross the threshold into pathology? Specifically in depression, this question can be formulated as, how is the depressive state different from other instances of *low mood*?

Traditional psychiatry takes functionality as a point of departure in answering this question. However, recent philosophical efforts have also underlined the possibility of a difference in the *subjective experience* (the phenomenology) of depression. (Wilkinson, 2022)

This invites a bigger philosophical question on the nature and conceptualisation of moods. Heidegger noted that moods are a natural and necessary part of human existence and interaction with the world. "The mood has already disclosed, in every case, Being-in-the-world as a whole, and makes it possible first of all to direct oneself towards something." (Heidegger, 2010). Through moods, we impose meaning onto the world.

In this quote, Heidegger had, in fact, observed the interconnectedness of reward, emotions, and motivation. Indeed, the neurocircuitry that computes reward and aversion has been found to be independent of but also interdependent on the neurocircuitry that computes emotions. (Yao et al., 2020) The subcortical segment of the reward/aversion circuit comprises the nucleus accumbens (NAc), the caudate putamen, the amygdala, the hippocampus, the thalamus, and the hypothalamus. (Breiter and Gasic, 2004) Many of these structures, such as the thalamus and hypothalamus, play a role in emotional processing. However, it is the amygdala that is specifically crucial for emotional appraisal. Therefore, the amygdala is proposed as a key connection hotspot linking emotional and reward processing. (Murray, 2017)

One of the proposed psychological links between these processes is on the attentional level, where they might interact to determine how to allocate attentional resources. (Murray, 2007) *Reward* merges both goal-conduciveness and valence and is shown to have an impact on the categorisation of emotion. (Yao et al., 2020) As the two

processes may be interlinked rather than hierarchically connected, it is plausible that emotional processing could reciprocally influence reward processing.

Reward usually indicates a theoretical positive value derived partly from positive affect. Thus, unsurprisingly, another point of convergence between the two circuitries is found to be NAc, a hotspot for computing pleasure and a connective hub in the reward circuitry. (Kringelbach and Berridge, 2013; Yao et al., 2020) A stimulus conditioned to generate rewarding effects also generates positively valenced emotions through pleasure and positive affect. (Jackson and Cavanagh, 2023)

In addition to linking an organism's emotional state to a previously neutral stimulus, reward processing also acts as the information backbone of motivated behaviour. (Breiter and Gasic, 2004) Thus, it sits at the centre of emotional states and motivated behaviour.

As expounded by the DSM-5 and the Hamilton Depression Rating Scale, which is regularly used to assess the severity of the patient's depressive state in clinical settings, low mood is defined as the persistence of negative affect. However, negative affect is not necessary nor sufficient for the diagnosis of Major Depressive Disorder (MDD). Notably, the presence of loss of interest or pleasure without low mood may still fall under the MDD diagnosis umbrella. As Heidegger and philosophers of psychiatry have elaborated, mood is an all-encompassing feature of the human mind that bridges the self with the world. A mood disorder, as in when moods are *pathological,* should and does encompass the vigour and direction of motivated action, valuation systems, associations, etc.

This is why reward processing—with its multifaceted nature and extensive neurocircuitry, much like the all-encompassing quality of moods—may serve as a mechanism to address the diverse symptoms of depression, given its conceptual integration of action and valence appraisals.

Chapter II: Anhedonia's Web of Depression -Reward Processing as a Target

The focus of the question now shifts from a conceptual exploration to a potentially scientific inquiry. And in fact, there does appear to be a dysfunction in reward processing in MDD. Neuroimaging studies have consistently implicated regions involved in the various components of reward processing, chiefly the striatum, in depressed patients. During reward tasks, the striatum and prefrontal regions believed to represent reward value are less activated than healthy controls. (Pizzagalli, 2023; Der-Avakian & Markou, 2012; Keren et al., 2018) Behavioural data corroborates neuroimaging studies. Depressed individuals exert less effort for reward and are less inclined to learn policies that will bring them reward. (Treadway and Zald, 2013; Pizzagalli, 2023) Interestingly, their behaviour also appears to be less influenced by reward. (Halahakoon et al., 2020)

As discussed previously, many depressed patients report losing interest and feeling of pleasure. This symptom is categorised as anhedonia, Greek for *without pleasure*.

In traditional therapeutic frameworks for depression, the symptom of anhedonia is addressed indirectly. Current treatment methods are able to address the persistence of negative affect in emotional processing successfully. (Harmer, 2008) In depression, negatively valenced information is prioritised, causing negative bias in emotional processing. (Harmer, 2008; Beck, 2002) Successful treatment methods, including Selective Serotonin Reuptake Inhibitors (SSRIs) and Cognitive Behavioural Therapy (CBT), all address this underlying issue in depression. Cognitive Behavioural Therapy is designed to address negative bias in depression cognitively, meanwhile, SSRIs address negative bias by way of regulating amygdala response. (Godlewska and Harmer, 2021; Warren et al., 2015) In fact, the failure to alleviate negative bias, to an extent, predicts poor treatment outcomes. (Godlewska and Harmer, 2021; Warren et al., 2015) Arguably, the neuropsychological success of the treatment methods mentioned hinges on addressing negative bias.

Neuroanatomically, the circuitry of pleasure appears to be evolutionarily well-conserved. (Kringelbach and Berridge, 2013) However, due to encephalization, there are direct descending pathways from cortical to subcortical regions in humans and other primates. (Kringelbach and Berridge, 2013) Therefore, subcortical computations, including pleasure, are susceptible to top-down regulation. More specifically, the NAc, a pleasure hotspot, which plays a *causal* role in the computation of pleasure, can be retuned to some extent through dopaminergic neurons. (Kringelbach and Berridge, 2013) As a result, pleasure is a somewhat flexible construct in the primate brain. Negatively valenced biases could be impacting the computation of pleasure through this flexibility.

Computational accounts of reward processing hint at the role of the associationistic framework that an object or action that is assumed to be pleasurable plays a role in the culmination of anhedonia. (Huys and Browning, 2021) While a healthy control might find watching their favourite series enjoyable, a depressed patient might attribute this action to unaddressed responsibilities and thus associate guilt and shame. This, in turn, could impact how much pleasure is derived from that particular event. Pleasure in the outside world exists not as a singular object/action but rather within a framework of associations.

In some sense, the associationistic framework echoes the concept of negative bias and may illuminate the psychological mechanism through which it operates. Depressed individuals are more likely to associate negatively-valenced attributes with a potentially positively-valenced object or action; thus, their enjoyment level is reduced.

Though surprisingly, SSRIs or CBT are ineffective in regulating deficits in reward processing in MDD; in fact, treatment with SSRIs may exacerbate certain anhedonic features. (Rush et al., 2006) While behavioural research has found acute and subacute reward processing dysfunction with SSRIs, fMRI studies have found decreased neural activation for rewarding imagery. (McCabe et al., 2010) Anhedonic symptoms have been found to be associated with lower responses to traditional pharmacological and psychological therapeutic approaches, as well as good predictors of a recurrence in depressive episodes. (Pizzagalli, 2023) In a similar vein, anhedonia itself is usually left

untreated, even if other depressive symptoms subside. (Pizzagalli, 2023) All in all, there are valid reasons to consider addressing anhedonia and reward processing as alternative treatment targets for depression. Merely focusing on symptoms of anhedonia through emotional processing targets appears inadequate.

Then arises the question of the precise approach to treating anhedonia.

When answering questions about pleasure, rather than assessing the current feeling, the patient is computing a theoretical salience and magnitude to a theoretical pleasure. Both of these computations are important for reward processing at large, which in some sense is a circuitry that encompasses pleasure and integrates feelings of pleasure to other cognitive processes. Thus, even though the definition itself might direct us to the construct of pleasure, the context by which it is computed points to the more extensive process that involves its integration. The symptom of anhedonia involves a neural circuit broader than that dedicated solely to pleasure. In fact, lowered response to reward and reduced activation of reward circuitries in neuroimaging studies are a reliable predictor of anhedonia. (Pizzagalli, 2023)

In current discourse, reward processing has been separated into three distinct but overlapping components: wanting, liking, and learning.[1] The three are argued to be distinguished phenomenologically, functionally, and neuroanatomically. (Berridge et al., 2009) In the traditional and colloquial usage of the word, pleasure has been collapsed to the liking component of reward processing in this account.

Ecological assessments and laboratory-based studies corroborate parsing reward processing components in depression and implicate each to different degrees. (Pizzagalli, 2023) In lab-based assessments where healthy control and depressed patients were asked to report pleasure based on gustatory stimuli, found no statistical significance. However, depressed patients needed more evidence to rate the same level of pleasure. (Borsini et al., 2020; Pizzagalli, 2023) Similarly, when asked to self-report the feeling of pleasure during day-to-day activities, most of the rigorous studies that successfully parsed between the three components, meaning they minimised reports based on prediction or memory, found that depressive individuals enjoyed the same activities to the same

[1] In this chapter, the difference between the subjective feeling of wanting and liking, and the objective (unconscious) behavioural output of wanting and liking will not be separated from one another.

degree. (Pizzagalli, 2023) Interestingly, in some instances, depressed patients even reported *increased* levels of pleasure.

These findings culminated in the launching of a different CBT approach called Behavioural Activation Theory (BAT). In BAT, depressed individuals are asked to participate in activities that they believe will bring them joy, following the hypothesis that they engage in pleasurable activities less frequently, culminating in anhedonia. (van Roekel et al., 2015) Compared to other CBT methods, BAT has been found to address anhedonia most effectively. (Pizzagalli, 2023) BAT's success has led to the hypothesis that anhedonia in depression could be more closely linked with other components in reward processing than pleasure itself.

Depressed individuals are less inclined to exert effort for higher rewards and have trouble learning policies that would get them the said reward. (Treadway et al., 2012) All of this, there is more evidence of a dysfunction in the *wanting* and *learning* components of reward processing in depression. Similarly, when participating in tasks that distinguish between *anticipation* and *consummation*, another way to parse reward processing, the NAc of depressed patients was less activated, especially during anticipation of reward, but also during the consummation. (Pizzagalli, 2009; Dillon et al., 2009) Though criticisms have been made in regard to insufficient differentiation between liking and learning in the consummation phase. (Pizzagalli, 2023) There is also evidence of impaired reward learning. (Halahakoon et al., 2020) However, the way in which behavioural tasks parse between components of reward processing appears controversial. Meanwhile, fMRI as a neuroimaging tool has low temporal resolution, exacerbating the issues of fully implicating one component versus another, given they are all interdependent.

While reward processing at large is distinctly, and to an extent independently, dysfunctional in depression, there is some controversy about which components drive this dysfunction. Better behavioural tasks that parse the different elements will allow for better conjectures.

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Another way to potentially address reward processing dysfunction in depression could be neurobiological intervention.

In depression research, anhedonia is sometimes intentionally induced for study purposes. Multiple animal models that research depression have found that anhedonia can play a causal role in the manifestation of depressive symptoms. (Anisman and Matheson, 2005) In addition to positively valenced circuitries, reward circuitries have also been found to overlap with the stress circuitry. (Pizzagalli, 2023; Fonzo, 2018) With recurrent induced stress, the animal can become *anhedonic* and present other depressive symptoms. (Anisman and Matheson, 2005)

Similarly, studies in adolescents and children corroborate the link between stress, anhedonia and depression. Early life adversity is linked with increased levels of stress during development. Longitudinal studies have shown that adults who have experienced early life adversity are more likely to have reduced activity during reward processing and self-report anhedonic symptoms. (Pizzagalli, 2023; Bolton et al., 2018) Overall, the preclinical and clinical models have resulted in the conceptualisation illustrated in Figure 1.

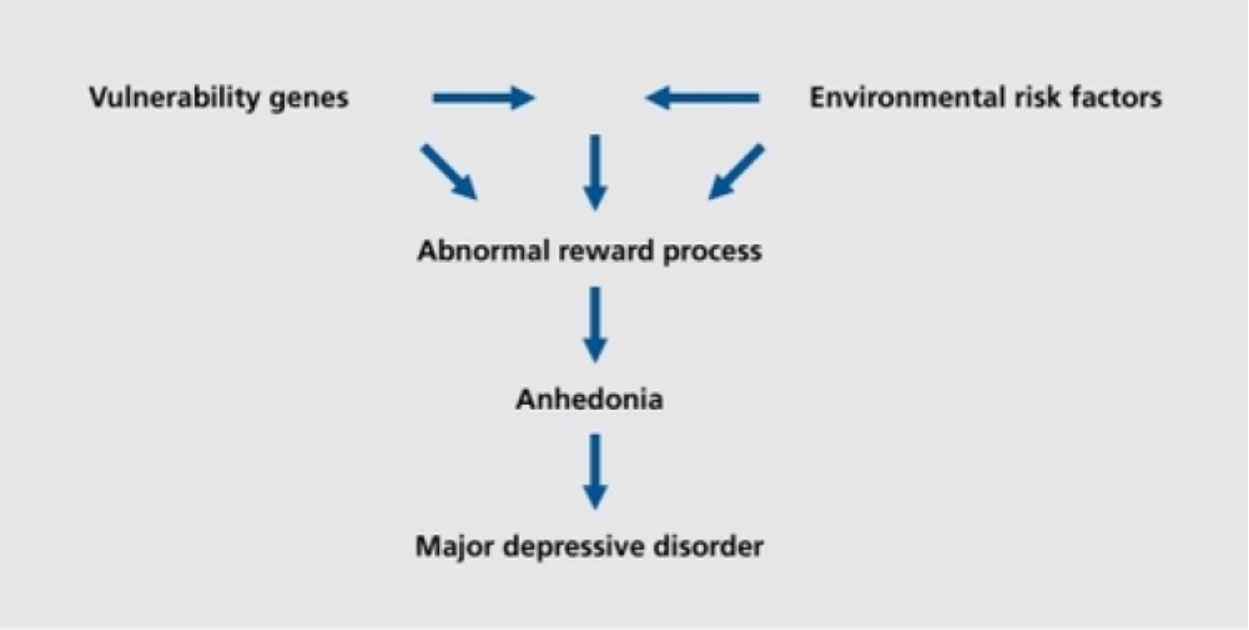

Figure 1: A theoretical model proposing the origin or causation of depression, explicitly highlighting anhedonia as a contributing factor.

Numerous comprehensive investigations focused on establishing a neurobiological explanation for the connection between anhedonia, depression, and stress in both preclinical and clinical models. These studies have consistently attributed a causal role to the same neural circuitry in maintaining this link: the mesolimbic dopaminergic circuitry. (Stanton et al. 2019)

Anhedonic individuals that have been through ELA show decreased dopamine levels during PET scans, especially in the NAc. (Fitzgerald et al., 2017) More invasive tests in preclinical models show reduced signalling in this circuitry as a good predictor of anhedonic behaviour. (Wang et al., 2021) Though this could only be true in cases where anhedonia precedes depression and is induced by way of stress in the developing brain, it remains as one of the best elucidated neurobiological models of anhedonia. In cases where anhedonia is central and cannot be resolved through other mechanisms, this model could be more relevant than any other. However, given the variation in anhedonia across and within diagnoses, a comprehensive and all-encompassing model of its neurobiological basis will remain elusive until rigorous subtypes.

Chapter III: Reward Circuitry Through Dopamine

While preclinical and clinical models may hint at the therapeutic potential of dopamine, this discovery hardly surprises most researchers in the realm of reward processing. The history of comprehending dopamine's role in the brain is intricately woven into the larger narrative of unravelling reward processing. Although the intricacies of its function remain a complex subject, its fundamental role appears in reward processing. To propose methods for manipulating dopamine in the brain, it is essential first to comprehend potential ways in which it might be influencing the reward system. To achieve this, it is crucial to thoroughly explore the role of dopamine within diverse investigative frameworks and conceptualisations of reward processing to interpret the findings adequately.

Dopamine's Odyssey Through Time

This section will focus on the previous perspectives on the role of dopamine and dopaminergic neurons, accompanied by the evidence supporting them, with historical accounts of the perspectives providing background context.

Dopamine's first discovery as an agent in motor-related functions led to classifying dopamine as a neurotransmitter in its own right. (Björklund and Dunnet, 2007) In Parkinson's, the neurons of the substantia nigra, one of the hubs for the synthesis of dopamine in the midbrain portion of the brain stem, slowly degenerate and lose their capacity of synthesising dopamine. (Bloem et al., 2021) By contrast, in Huntington's Disease, the mutant version of the gene HTT causes the degeneration of certain neurons in the basal ganglia. Initially, this causes an increase in dopamine levels. (Walker, 2007) In PD, lower levels of dopamine are associated with hypokinesia, slowing of movements, whereas in Huntington's Disease, the initial high levels of dopamine result in hyperkinesia, excessive involuntary movement. Thus, it was deemed clear from these two opposite illnesses that dopamine is related to controlling movement, therefore enabling the cognitive governance of motor-related afferent systems, but can also be associated with the *vigour* of the said movement.

Subsequent research revealed that dopamine's role extended beyond voluntary movement to include significant involvement in reward processing. This expanded role is supported by the regulation of various neurons and pathways by dopamine, with four major pathways (nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular) alongside numerous smaller ones. While the nigrostriatal pathway primarily coordinates voluntary movement, other pathways serve different functions and have distinct input-output regions in the brain. Even the nigrostriatal pathway has been found to play a role beyond movement. (Horvitz, 2000; Wise, 2009)

Hindsight makes this finding unsurprising. Voluntary movement involves more than coordinated actions and afferent motor signals. In both animals and humans, actions go beyond simple stimulus-response. Motivation is multifaceted, driven by

long-term goals and curiosity. Thus, dopamine's role in linking cognition and action is intricate, extending beyond mere coordination.

A significant restriction on the computation of directed action is *valuation*. At a certain point, before coordinating the action, upstream neurons must compute and compare the values of a set of actions.

Then the question is, how does the brain compute 'value' or even define it?

The Research Domain Criteria, which aims to map the psychological domains of the mind onto the neurophysiological domains of the brain, conceptualises value under the sub-construct 'reward valuation', which can be found under the positive valence system. Schultz comprehensively illustrates reward as "**objects** or **events** that generate **approach** and **consummatory** behaviour, produce **learning** of such behaviour, represent **positive** outcomes of economic decisions and engage positive emotions and **hedonic** feelings." (Schultz, 2010)

One of the first inspirations for the research implicating dopamine in reward processing put electrodes into rat brains and connected them to a lever in 1952. The rats exerted physical effort for the electrical stimulation, especially in the septal area. (Olds and Milner, 1954) Thus, that particular localisation of electrical stimulation and voluntary action was proposed to be linked, though the exact nature of the link needed to be understood.

Later studies that used psychostimulants -such as amphetamine and cocaine- saw that behavioural data obtained from these pharmacological interventions mimicked the findings of brain stimulations of the septal area. (Kuhn et al., 2019; D'Souza and Markou, 2010) With both pharmacological interventions, research in mice showed that usage of psychostimulants, such as cocaine and methamphetamine, increased voluntary movement and operant conditioning of stimuli, acted as a reinforcer of further drug use, and decreased thresholds for reinforcing brain stimulation. (Kuhn et al., 2019; D'Souza and Markou, 2010) These findings, especially the latter, imply a convergence between the pathways affected by the stimulation and psychostimulants. There comes a point where the representations altered by septal electrical stimulation and psychostimulants intersect, leading to one intervention affecting the other.

Yet, these psychostimulants affected various pathways of different neurotransmitters. Research with injecting haloperidol, a dopamine antagonist, into the nucleus accumbens of mice supported the reward-related behavioural findings; they consistently showed reduced directed action and consumption of reward. (Berridge and Robinson, 1998; Negrelli et al., 2020) Later findings showed that all reward-affecting psychostimulants and electrical stimulations converged on the dopaminergic pathway to the nucleus accumbens from the VTA. (Olguín et al., 2016) Thus, dopamine was the culprit responsible for the behavioural output observed in the localised electrical stimulation experiments. In fact, without dopamine transporter inhibition (which increased the dopamine's concentration and time in the synaptic cleft), cocaine did not produce reinforcing effects. (Hall et al., 2004)

However, reward involves many constructs, as mentioned above. The field of neuroscience and psychology often employs a somewhat top-down approach to understanding processes within the mind. In this approach, researchers aim to distil neurobehavioural findings from concepts influenced by sociocultural factors. Affective research exemplifies this paradigm.

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Before adopting the intellectual attitude of approaching human behaviour and mind from a scientific perspective, the word *reward* was still a part of daily language, used interchangeably with *pleasure.* (Marks, 2011) The echoes of this conceptualisation reverberated in interpreting the behavioural data of reward-related research. The entirety of *reward* had been collapsed to the hedonic aspect of reward, the most phenomenologically salient one. Psychostimulants made people more responsive to reward *because* their hedonic capacity had increased. Simultaneously, the role of the neurotransmitter more rigorously linked with reward, dopamine, was also collapsed to pleasure. (For a detailed account of this view, see: 'The Anhedonia Hypothesis' by Wise)

Then came Herbert Spencer and his *Principles of Psychology*. In this book, he proposed that reward-based (what he generally meant was pleasure-based) learning is an evolutionary adaptation. (Spencer, 1896) This mirrored the sentiment of his time that was more and more acclimating to a functionalist approach (i.e. explaining biological

phenomena through their adaptive function) after the entrenchment of evolution.[2] This, in turn, led to B.F. Skinner's behaviourist formulation: "Rewards select the behaviour that precedes them." (Marks, 2011)

However, there was a certain circularity to this formulation: “Effects are produced by rewards but then are defined by their effects.” (Marks, 2011) In an attempt to explain *how* reinforcers reinforce, behaviourist Hull merged Fencher’s constancy principle (a preliminary hypothesis that merged desire with homeostatic regulation) with Freud’s pleasure principle. (Marks, 2011) A biological need, causes a *drive*, which in turn creates rewards that reduce the drive. (Hull, 1943)

Hull’s theory saw many updates. Olds and Milner’s research, as mentioned earlier, which came after Hull’s formulation, showed that reward was not only involved in reducing a biophysical need but was *sufficient* to drive action. In a similar vein, “reduction in a driving stimulus may be sufficient for reward but is not necessary.” (Marks, 2011) Efforts to understand the role of curiosity and how it impacted action saw that perhaps psychological needs, such as reducing unpredictability, also drove action. (Murayama et al., 2019)

Yet, one thing remained constant: The behaviouralist accounts had reduced *reward* to its role as a *reinforcer*. When combined with the pharmacological and electrophysiological implications of dopamine in the reward circuitry, research that formally explored dopamine's role in reward processing framed itself around its involvement in reinforcement learning. (Schultz, 2002)

Framing Current Perspectives on Dopamine with a 'Marr'velous Twist

The question now is, what is the current perspective of the role of dopamine? With the advent of technology and mechanical information-processing systems, our current source of inspiration by which behavioural data and neurobiological findings are tied is computers. A framework elegantly expounded by Marr captures and harnesses this perspective. In summary, Marr, a neuroscientist with an engineering background,

[2] “Functionalism begat behaviourism.” (Marks, 2011)

proposed that there are three levels of analysis to any information-processing system after his work on the visual system: the computational (input to output), the algorithmic (what is the algorithm to transform the input to the output), and the implementation (physical realisation and hardware that gives rise to the algorithm). (Marr, 2010)[3]

By utilising this framework, we can summarise the ongoing questions about dopamine and the current perspectives about its role in reward processing. Schultz and Wise's research that formally implicated dopamine in reward processing proposed that the phasic levels of dopamine in the ventral tegmental area and substantia nigra compute scalar reward prediction errors, where the difference between expected/predicted reward and received reward extinguishes or reinforces a given behaviour. (Schultz et al., 1997; Schultz, 2017; Wise and Bozarth, 1984) In their highly replicated research, levels of dopamine phasic signalling increase with positive reward prediction error (more reward than expected), remain the same with no net prediction error and are depressed with negative reward prediction error (less reward than expected). (Schultz et al., 1997) Moreover, the plasticity of the neurons involved in learned behaviour is modulated chiefly by the mesolimbic dopaminergic pathway. (Zhang et al., 2009; Sanyal et al., 2004) Reward processing and its relationship with dopamine signals have been proposed as a 'poster child' for the success of Marr's framework. (Niv and Langdon, 2017)

Nonetheless, recent research undermines the straightforward conceptualisations significantly. The evolutionary perspective on psychology allows us to establish a normativity to the desires of biological organisms and their goals, thus allowing us to establish normativity to rewards as well. By doing so, in neuropsychological research, we have a norm to impose on the computational level: A starved rat must have an *inclination* to eat the food given in order to survive. We can then loosely define computational-level goals of reward processing asmaximise reward and punishment, as well as decrease the uncertainty of reward. (Niv and Langdon, 2017) By increasing

[3] Whether this is a 'right' approach is beyond the scope of this dissertation or literature review. Yet, one must admit, it is an empirically fruitful one. It is also one that permeates the field.

positive valence and decreasing *negative* valence in a decision-making system, the organism will be more prone to be engaged and, hence, survive.

This brings us to the second level, the algorithmic level. A few essential algorithmic challenges are relevant to reinforcement learning. For one, the system must assign the correct outcome to the correct previous action or state. Secondly, it must flexibly update the values of specific actions or states. Thirdly, it must predict the temporal relationship between the state/action and the reinforcer. Finally, it must decide how much the decision-making system should 'assign a value' to that particular action/state in the first place. (Niv and Langdon, 2017)

Proponents of Marr's organisational framework have tried to pin down composite algorithms to specific neural processes. As described above, dopamine presented itself as a straightforward answer to the algorithmic question of updating rewards. However, biological variations in dopamine receptors and pathways contradict this reductionist account. For one, dopamine neurons also encode for salient but non-rewarding experiences, i.e. alerting and aversive stimuli. (Matsumoto and Hikosaka, 2011) Figure 2 shows Matsumoto and Hikosaka's hypothesis for depicting the two dopaminergic reward pathways, one involved in computing *motivational value* and the other engaged in computing *motivational salience*, two related but distinct constructs.

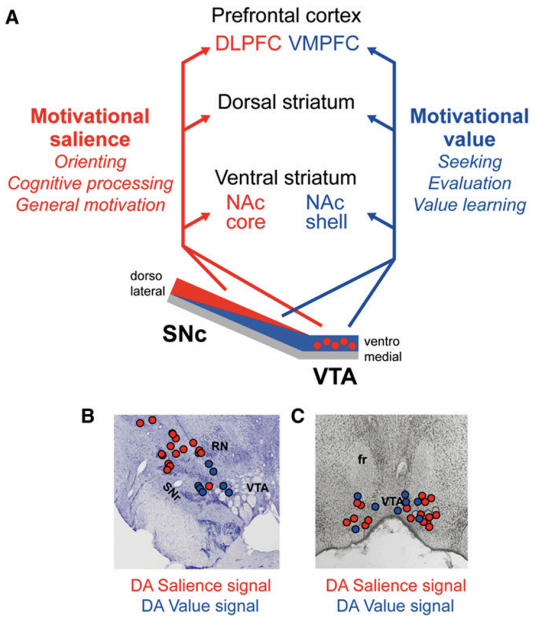

Figure 2: Depiction of the two parallel dopaminergic streams that encode two different properties. The dorsal pathway encodes for salience, while the ventral pathway encodes for reward.

Primate research has shown that while the ventral striatum has downstream effects on a wide range of dopamine neurons and is itself only influenced by a small number of them, the opposite is true for the dorsolateral striatum. (Haber and Knutson, 2010) These two separate reward streams also have different functional and

anatomical connectivities and molecular compositions. (Haber and Knutson, 2010) Thus, while implicated in reward processing, dopamine has a variety of functions in modulating and integrating the computations involving reward into other processes.

This is unsurprising given the reward's role in psychological processes. Not only does it integrate pleasure and other valence systems into memory and predictive processes in its evaluation, but it also integrates motor and cognitive processes to coordinate and select actions as a response.

Furthermore, research regarding dopamine's role in reward learning has also been undermined by recent perspectives on behavioural data from previous research. While dopamine's implication in reward processing has predominantly centred on its impact on reward learning, emerging evidence suggests that dopamine may primarily play a crucial role in another facet of the reward system. In a paper published in 1998, Berridge and Robinson dissociated reward into three distinct computations: wanting, liking, and learning. While the three are interdependent, neuroimaging data allows us to distinguish between the three processes, with distinctive brain region activity corresponding to the distinctive computations across mammalian brains. (Berridge et al., 2009)

Current research points to dopamine's role in the *wanting* construct of reward processing rather than learning or liking. Schultz and Wise's research that catapulted the implication of dopamine in reinforcement learning used intracranial recordings. A major drawback of this method is its inability to establish causality between neural activity and behavioural function. The neuron might simply be responding to previous neuronal computations and not encode for the reward prediction error itself. Thus, dopamine could be a representative agent and not a causal agent in reward prediction errors. (Schultz, personal communication to Berridge, May 2006) The consensus seems to be that dopamine in the VTA, and SNc is on the pathway for encoding reward prediction errors. (Dailly et al., 2004; Nestler and Carlezon, 2006; Schultz, 2007; Lerner et al., 2021) Yet, according to Berridge, it is neither necessary and/or sufficient for the computation.

Mice studies with a mutant gene disabling them from catalysing dopamine production and their unchanged levels of updating values support this conjecture.

(Berridge and Robinson, 1998) However, the brain is a dynamic system and could compensate for the lack of dopamine with other neurotransmitters and their neurons in the same region to the same effect. The VTA is a highly heterogeneous region, and its neurons also release GABA and glutamate. (Morales and Margolis, 2017) In addition, the mutant mice required caffeine to update their values through reinforcement learning. (Berridge and Robinson, 1998) Without resorting to dopamine, an external agent became necessary for efficiently calibrating the brain. Due to the significant evolutionary importance of encoding rewards, it is possible that seeking causality through a single neurotransmitter and pathway could be limiting. Additionally, the study solely relied on behavioural data to measure reinforcement learning. Caffeine, known to have a broad impact on the brain, might have influenced various processes like attention and wakefulness, potentially leading to similar outcomes through different algorithms. Dopamine inherently encodes reward prediction errors; however, it is conceivable that alternative neurotransmitters engaged in reward processing, particularly glutamate neurons in the ventral tegmental area (VTA), might assume its function.

Moreover, dopamine transporter (DAT) knockout mice showed a 170 % increase in extracellular levels of dopamine and an unchanged response rate in reward learning. (Berridge and Robinson, 1998) Nonetheless, it is unclear whether phasic and tonic dopamine signalling rates coincide with increased extracellular levels of dopamine in the same way. (Berridge and Robinson, 1998)

Berridge uses all of these arguments to support the idea that dopaminergic neurons in reward processing that encode for RPEs are a *consequence* of the upstream computations that are actually causally linked with the RPE computation. Thus, an argument implicating dopamine in a different reward-related construct *-wanting-* is built. (Berridge et al., 2009; Berridge and Robinson, 1998)

The mice unable to produce dopamine did not seek out drinking or eating, but when they did drink sucrose water, it was in higher quantity than control -possibly because they were hungrier. (Berridge et al., 2009; Berridge and Robinson, 1998) Similarly, the mice with hyperdopaminergic levels had increased reward-seeking and consuming behaviour. (Berridge et al., 2009; Berridge and Robinson, 1998) While this

account of the literature appears convincing, it has a few caveats: System-level and molecular compensatory mechanisms might confound the apprehension of especially behavioural data, which answer questions relating to a construct primarily on a computational level.

Overall, the top-down approach of computational to implementation levels in reward-processing research, and especially reinforcement learning, has brought forth a beautiful but flawed account of dopamine's role in reward processing. The approach itself enabled a reductionist theorising on dopamine's role in the central nervous system. Yet, dopaminergic pathways are differentiated by a multitude of factors, not excluding receptor subtypes, localisation, functional and anatomic connectivity, and even molecular composition.

Although traditional understandings of reward have conflated it with pleasure, behaviourist findings have reduced it to reinforcement. Similarly, the current trend in reward processing appears to be apprehending the *wanting* aspect of reward. The question of how stimuli drive voluntary action has been fundamental throughout human existence in different modes. Currently, reward has a new and flexible -thus more comprehensive- definition as a "motivational magnet." (Kringelbach and Berridge, 2016) Yet, this definition also favours one aspect of reward more than others: wanting.

Chapter IV: Assembling the Puzzle

The previous chapter aimed to put forth how the deconstruction of reward processing shapes what causal role is attributed to dopamine. While more research that allows dopamine to speak for itself might answer the open questions, clinical usefulness[4] can be established through experiments that explain what would happen to certain relevant psychological constructs when its level in the human brain is globally increased. To that end, it is a more straightforward input-output question at the computational

[4] In the case of this study the potential for clinical usefulness

level which behavioural data can answer. Though this would not predict or explain the patient's potential neuropsychological response, it could still act as a proof of concept.

Increasing dopamine results predominantly in the seeking of and acting on reward. (Berridge et al., 2009; Berridge and Robinson, 1998) In a similar vein, research that tested reward learning in mice treated with haloperidol, a dopamine antagonist, saw an increase in the extinguishing of reinforcement learning without the chance of computing RPEs, i.e. before interacting with the reward. (Pizzagalli, 2023) Berridge's answer to this behavioural finding has been to propose dopamine as a liaison between the hedonic evaluation of stimuli and the assignment of this value to certain objects and acts, which he succinctly labelled as 'incentive salience.' (Berridge et al., 2009; Berridge and Robinson, 1998) Despite criticisms of this view, there is an agreement on dopamine signalling acting as a *necessary* link between evaluating potential rewards and the policy (sequence of actions) that acquires the reward. (Egelman et al., 1998; Coddington et al., 2023; Suri, 2002) One experiment tested inhibiting the VTA dopaminergic spikes and blocking dopamine binding in the NAc in mice and showed a similar disruption in reward processing. (Fig. 3) (Montague et al., 2004) The mice were trained to run across a maze to receive sucrose water. Yet, compared to the control group, both groups were less active and chose not to run through the maze. However when the sucrose water was moved closer to the mice, there was no difference in the amount of consumption. Similar experiments with dopamine antagonists-treated mice showed that the test group

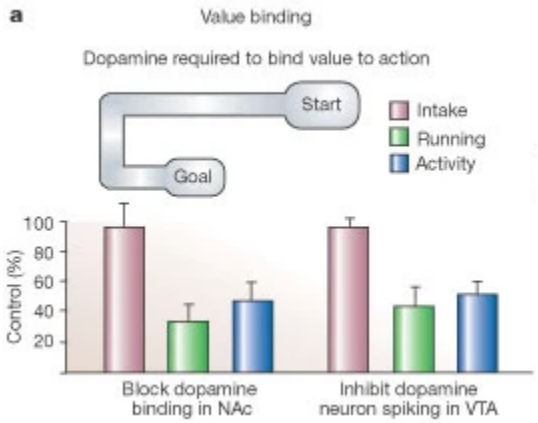

Figure 3: Rats trained to navigate a maze for sugary water show reduced activity when dopaminergic spiking is blocked in the VTA (left histograms). While the hedonic value of the water is computed, the connection to the necessary actions for obtaining it is impaired. Similar effects occur when dopamine's interaction with its receptor is blocked in downstream targets (right histograms).

was unable to sequentially link actions to obtain rewards. (Saunders and Robinson, 2012)

The research on humans with dopamine precursors (L-Dopa) echoes the findings in mice behavioural paradigms, where alterations in the acute reward processing due to pharmacological intervention resulted in a higher selection of rewarding actions. (Pessiglione et. al, 2006; Wunderlich et al., 2012) Though only a few, some null findings relating to L-Dopa can be found in the literature, but many are criticised based on methodological errors and small sample size. (Soutschek et al., 2021)[5] With D2/3 antagonists, however, participants showed reduced cue-induced responding and increased reward impulsivity. (Weber et al. 2016) The increase in impulsivity is worth exploring whether it is due to psychological or molecular compensatory mechanisms or whether the D2/3 receptor family has a modulatory role in reward processing.

Another recent comprehensive study with pramipexole, a D2-agonist, combines behavioural data to address the computational level, computational paradigms to address the algorithmic pharmacological intervention and the fMRI data for the implementation level. (Halahakoon et al., 2023) Previous research on acute administration of the D2 receptor agonist pramipexole has looked at reward-related neural responses. There was blunted activation in regions implicated in encoding positive outcomes, mainly mPFC, OFC, VS, and the midbrain. (Riba et al., 2008; McCabe et al., 2010) After observing healthy volunteers and their neurobehavioural responses for two consecutive weeks, researchers decreased the difference between win and no-win outcomes and better performance at reward valuation tasks. Interestingly enough, pramipexole has been found also to decrease neural activation to RPEs in vmPFC while increasing the reactivity of the OFC in anticipation of reward. By feeding this pattern into computational paradigms, it was thus proposed that the change in behavioural patterns was due to the decrease in decaying value and that the expectation/estimation of reward value was maintained. Another important finding was that no change was associated with the computation of loss trials, supporting the

[5] It is worth keeping in mind the effect of publication bias in the literature in relation to dopamine's positive relation in reward processing. (Halahakoon et al., 2020)

premise that dopamine and reward are more involved in maintaining positive affect than reducing negative affect. (Halahakoon et al., 2023)

The discrepancy between acute and longitudinal findings could be due to a few factors. One is the pharmacological properties of pramipexole: as a D2/3 agonist, it is known to also bind to dopamine autoreceptors, perhaps prematurely signalling to the neuron to stop releasing dopamine. (Voon et al., 2017) Two, pramipexole's effects might become more salient due to functional and anatomical synaptic plasticity. Thirdly, the differentiation between pleasure and aversive signalling in NAc relies on D2 signalling. If D1 is activated, positive valence is encoded, whereas if D1 and D2 are both activated, then negative valence is encoded. (Berridge and Kringelbach, 2013) Thus, D2 activation in pramipexole could have initially increased the D2 signalling in NAc, creating a negative bias.

As can be seen, an overarching issue with pharmacological research is the global effects of the medication on a variety of pathways or undesired preferences of specific receptor subtypes. Research that couples pharmacological intervention and neuroimaging methods with a computational backdrop can thus allow us to link all three levels of Marr's analysis to a satisfactory extent to propose comprehensive theories on the psychological effects of medication. Additionally, the diversity of pharmacological actions is a significant confounder in assigning dopamine with a global computational role in reward processing, and it is more scientifically credible to assign a computational role to a specific *medication* than the varied systems it is thought to impact when relying on pharmacological and behavioural data.

Chapter V: The Revival of MAO Inhibitors

The earliest antidepressant, iproniazid, functions as a monoamine oxidase (MAO) inhibitor. These inhibitors work by blocking mitochondrial enzymes responsible for the oxidative deamination of a wide range of amines, including various neurotransmitters. Consequently, this action elevates the concentrations of these amines. (Cesura, 2007)

The antidepressant effect of MAO inhibition was discovered serendipitously in the 1950s during a clinical trial of iproniazid for tuberculosis. Subsequent efforts confirmed its antidepressant properties with placebo-controlled trials. However, in the 1980s, soon after the discovery of selective serotonin-reuptake inhibitors (SSRIs), MAO inhibitors such as iproniazid were scrapped as first-line antidepressants. Despite their promising efficacy, they had significant limitations primarily because of their interactions with food, more colloquially known as the 'cheese effect.' (Knoll, 1979; Knoll, 1993). The monoamine oxidases in the gastrointestinal system typically metabolise tyramine. Therefore, the global inhibition of MAO leads to a substantial increase in tyramine levels. Tyramine is important in the cardiorespiratory system, mainly since it can displace noradrenaline and other monoamines. (Knoll, 1979) Unfortunately, when MAO inhibition is combined with dairy products or other foods high in tyramine, the subsequent increase in tyramine levels can result in hypertension.

Then came the 1962 drug l-deprenyl, also known as selegiline. Selegiline was the only MAO inhibitor devoid of the "cheese effect" since it did not interact with a particular class of the gastrointestinal system MAO inhibitors. (Gerlach et al., 1996) Nature has distinctly divided monoamine oxidases into two isoenzymes, each encoded separately in the genome and exhibiting unique substrate preferences. Knoll (1979) elucidated this differentiation by demonstrating their responsiveness to specific inhibitory molecules. Clorgyline inhibited MAO-A, while selegiline inhibited MAO-B, though the underlying inhibition mechanism remained the same. These findings underscored the active site's divergence in the substrate recognition section rather than the catalytic region. Subsequent crystallography studies corroborated this hypothesis, revealing that the catalytic sites of the two isoforms, consisting of an aromatic cage composed of the FAD coenzymes and two tyrosines, were identical. (De Colibus et al., 2005) Conversely, the substrate recognition sites exhibited substantial differences: MAO-B possessed a broad yet shallow site, whereas MAO-A's site was deeper but narrower. Accordingly, the biochemical basis for their substrate preferences became evident; MAO-B favoured substrates with shorter side chains, such as dopamine and trace amines, while MAO-A exhibited a preference for those with longer side chains,

including serotonin and norepinephrine. However, it also exhibits a significant affinity to dopamine. (De Colibus et al., 2005)

Another important distinction between these two isoforms is their localisation in the body. MAO-A is found dominantly in the enterohepatic system and the locus coeruleus (though there is evidence that low levels of MAO-A mRNA are found in serotonergic neurons as well), whereas MAO-B is found mainly in the CNS, especially the serotonergic neurons in the raphe nucleus. (De Colibus et al., 2005) Intriguingly, according to immunohistochemistry research, the ratio of MAO-A to MAO-B is 1:4 in the human brain. (De Colibus et al., 2005) Instead of being intraneuronally situated, MAO-B is also found in the glial cells of dopaminergic neurons, and its concentration increases with age, possibly due to the proliferation of glial cells. (De Colibus et al., 2005; Shrivastaw et al., 1983) Overall, there appears to be some flexibility across organisms and species regarding the localisation of these two isoforms, and localisation itself is a significant mode of regulation of the activity of these enzymes.

Accordingly, the inhibition of MAO-B with selegiline was theorised to increase dopamine and other trace amines (especially phenylethylamine) levels in the CNS. In low doses, 0.25mg/kg, selegiline maintained its specificity to MAO-B. This theory has been corroborated by the findings of post-mortem, immunohistochemical, and positron emission tomography studies (Heinonen et al., 1994; Heinonen et al., 1991). In fact, it is also a fast-acting compound. Selegiline binds to almost all platelet MAO-B within the first hour of taking the 10 mg oral pill. (Heinonen et al., 1994; Heinonen et al., 1991) Postmortem studies on Parkinsonian patients reveal that nearly 90% of MAO activity on dopamine was inhibited after treatment with selegiline, which also correlated with increased dopamine concentration, especially in the nigrostriatal dopaminergic neurons. (Heinonen et al., 1994; Heinonen et al., 1991; Knoll, 1979)

While recent studies claim that MAO-A is the sole enzyme metabolising dopamine and that MAO-B is involved in GABA metabolism (Cho et al., 2021), it is essential to note that this research has been conducted on the rat brain, which has a MAO-A/MAO-B ratio of 1:1 in the CNS, exhibiting significantly different distributions. (De Colibus et al., 2005) Since localisation appears to be a significant

control mechanism for the activity of these two isoforms, generalising this data to humans should be treated with caution. Meanwhile, data from primate studies, which have very similar distributions of the two isoforms in the CNS to humans, corroborate the link between MAO-B activity and dopamine. (De Colibus et al., 2005)

The same research which claimed to undermine the role of MAO-B on dopamine also took note of the extracellular nature of the biochemical activity of MAO-B on dopaminergic neurons. (Cho et al., 2021) The glial cells surrounding dopaminergic neurons took the extraneuronal dopamine from the pre-synaptic neuron and inactivated it. Interestingly, some dopaminergic neurons have MAO-A, and all serotonergic neurons in the raphe nucleus have MAO-B intracellularly. Yet the inhibition of either does not increase dopamine and serotonin levels, respectively. Potentially, the extraneuronal mechanism of these two isoforms could be more directly related to the neurotransmitter concentration in the synaptic cleft. Given that intraneuronal levels of a neurotransmitter and the concentration to be released are strictly regulated by synaptic vesicle pools, the effects of intraneuronal MAO inhibitors could be subject to better compensatory mechanisms. (Greengard et al., 1993; Hua et al., 2011; Chanaday et al., 2018; Gitler et al., 2004)

Still, more research into the biochemical activity of especially MAO-B and its inhibitors is clearly needed. Moreover, the distinction between extraneuronal activity and intraneuronal activity of the two isoforms and how this relates to neurotransmitter levels in the synaptic cleft should be elucidated.

Additionally, the other biochemical pathways that involve MAO-B and selegiline should be elucidated further to reveal their full potential as an antidepressant. Selegiline also inhibits the reuptake of dopamine, increases its synthesis by binding to the autoreceptors, which would control the extraneuronal compensatory mechanisms, and has been theorised to have neuroprotective effects. However, there is a discrepancy between *in vivo* and *in vitro* studies. (Heinonen et al., 1994; Heinonen et al., 1991; Knoll and Magyar, 1977) Most of the biochemical research regarding MAO-B inhibition is conducted on Parkinsonian patients, where dopamine levels are abnormally low. For most depressed patients, this statement does not apply, suggesting that

compensatory mechanisms in this group may function differently when using selegiline compared to Parkinsonian patients. (Dunlop and Nemeroff, 2007)

Overall, selegiline's potentiation of dopamine is inferred with the reduced peripheral MAO-B platelet, its efficacy in Parkinson's, which is caused by low dopamine production, post-mortem findings of increased dopamine levels in dopamine-rich regions, and the findings relating dopaminergic neurons to MAO-B enzymes. (Knoll and Magyar, 1977; Heinonen et al., 1994) Most of selegiline's pharmacological properties have been expounded by research in Parkinson's patients and mice using older methods. Thus, new research incorporating newer imaging methods (i.e. PET scans) on healthy human brains with an emphasis on quantifying the change in dopamine levels will help us better assess selegiline's efficacy as an antidepressant.

Though not providing the complete picture, the available evidence indicates that selegiline enhances extracellular dopamine levels since it works extraneuronally on dopaminergic neurons. Even with this conceded point, another question of whether this biochemical change amounts to a functional and psychological change is even more ambiguous. Selegiline's antidepressant properties have been mainly tested with the transdermal patch application rather than the oral tablet—the pharmacokinetic mechanisms between the two result in different biochemical changes within the brain. The bioavailability of the parent drug and not its metabolites in STS is 73%, whereas the bioavailability of the oral delivery is only 4%, with a swift decline of peak plasma levels after 1 hour. (Azzaro et al., 2007) While the increase of the parent drug's bioavailability is essential, since selegiline's primary metabolites, r-methamphetamine, r-amphetamine, and demethylselegiline, are not found to be therapeutic, the increase in its bioavailability also causes it to lose its selectivity for MAO-B. (Finberg and Rabey, 2016)

Pooled statistical analysis of 5 placebo-controlled, double-blind studies has shown significant but modest effects when compared to placebo on patients suffering from atypical depression. (Patkar et al., 2014) However, testing on endogenous (melancholic) depression is less conclusive since there have been fewer trials of selegiline in this group. Studies researching the potential antidepressant properties of the oral pill have found

that the dose of the oral tablet should be high enough for the pill to lose its selectivity to dopamine to have therapeutic properties. (Morgan, 2007)

In summary, most of selegiline's efficacy in depression has been assessed via how it affects the serotonergic circuitries and thus, low dosages of selegiline, with an effect dominantly on dopamine levels, have been neglected as an alternative approach to depression therapeutics. Also, low-dose, selective, orally-administered selegiline's pharmacokinetics are better understood in elderly Parkinsonian patients. In conclusion, its usage as an antidepressant warrants more research directed towards (a) understanding its pharmacokinetic properties in patients without abnormally low dopamine levels in various age groups, (b) relate the pharmacological findings to neuronal activity in dopaminergic neurons, especially in humans and other animals with similar MAO-A and MAO-B distribution, (c) expound on the psychological effects caused by the alterations in neuronal activity.

An Eager Sentinel

I. Hypotheses

1. Acute administration of selegiline will positively impact reward processing, mainly through increased reward valuation and responsiveness compared to placebo administration.
2. Acute administration of selegiline will positively impact emotional processing through interactions between reward and emotional processing compared to placebo.

II. Research Design

To that end, I have conducted a placebo-controlled, double-blind, randomised, parallel-group study to assess selegiline's potential therapeutic capacity for depression and, more specifically, anhedonia. In this study, healthy volunteers conducted behavioural tasks that assessed different components of reward and emotional processing upon acute administration of either placebo or selegiline. Examining acute effects facilitates a more discerning analysis of the interplay between neurobiological and behavioural factors.

PART II:

The Acute Effects of A Single Dose (10 mg) of Selegiline on Emotional and Reward Processing in Healthy Volunteers

I. Ethical Approval

This study received ethical approval from the University of Oxford Medical Sciences IDREC. The study was carried out in alignment with the guidelines and principles outlined in the World Medical Association Declaration of Helsinki. All tested individuals signed a written informed consent for study participation.

II. Research Design:

This is a double-blind, randomised, parallel-group study with healthy volunteers and a sample size of 22. Participants were randomly allocated to either a placebo (an empty capsule) or 10 mg of selegiline (in a matched capsule) using a randomisation code generated by a researcher uninvolved in the study. The weight of the two capsules was not noticeably different. The data was acquired in the testing session.

A. Participant Screening

An opportunistic sampling strategy was used to recruit the participants from the general population. To assess preliminary eligibility based on predetermined criteria for the study, interested individuals filled out an online Qualtrics form. An initial online screening was then performed, which included the Structured Clinical Interview assessing DSM-IV Axis I psychiatric conditions (SCID-I) and gathering essential demographic information such as age, gender, medical history, concurrent medications, and drug use. All participants had to be aged between 18 and 40 years, have a Body Mass Index (BMI) above 17kg/m2, possess sufficient fluency in English to complete the psychometric testing, are without current drug or medication usage, and have no history of any DSM-IV

psychiatric illnesses, past or present. The study only enrolled subjects whose medical conditions would not pose a safety risk during the scientific assessment and were not on any medication, especially contraception pills, which have been found to interact with selegiline. Individuals with contraindications to selegiline, heavy smoking (>10 cigarettes per day), high caffeine consumption (>6 units per day), participation in other drug studies three months before this study, or prior experience with the reward tasks or ETB were excluded.

Participants who met the eligibility criteria in the screening and were willing to participate returned for the first and only test visit between one and four weeks after the initial screening, barring two because of previous recreational drug use. Before they participated in the testing session, it was ensured that they still met the eligibility criteria.

B. Testing Session

At the outset of the testing session, a comprehensive set of questionnaires based on self-report and one cognitive assessment were administered to the participants, aimed at quantifying various aspects of their psychological and emotional well-being. The Beck Depression Inventory (BDI) was the first of these questionnaires, and it was designed to gauge the severity of depressive symptoms experienced by each participant. The BDI score can range from 0-63: scoring between 0 and 9 suggests the absence of depression, while a range of 10 to 18 points to a condition of mild to moderate depression, scores falling within the 19 to 29 range are indicative of a moderate to severe level of depression, and a score of 30 or higher signifies severe depression. (Beck et al., 1961) Following the BDI, the Positive and Negative Affect Scale (PANAS) was delivered. This scale helped researchers discern the prevalent positive and negative emotions within each participant at the onset of the session. The scores for both Positive and Negative Affect can vary from 10 to 50, where lower scores signify lower levels and higher

scores signify higher levels of affect. (Watson et al., 1988) Later, the National Adult Reading Test (NART) was conducted to assess the participants' verbal intelligence. The scoring system relied on the calculation: Estimated Verbal Scale IQ = 128.7 – .89 × (Errors). (Nelson & Willison, 1991) The Eysenck Personality Questionnaire (EPQ) was introduced for an in-depth exploration of personality traits. It facilitated the early profiling of participants based on factors such as extraversion, neuroticism, and psychoticism. The maximum score for each scale is 12, while the minimum is 0. (Eysenck & Eysenck, 1963). Anxiety, a significant component of psychological well-being, was assessed through the State and Trait Anxiety Inventory (STAI). This inventory helped distinguish between immediate anxiety states and more enduring, trait-based anxiety tendencies in participants. STAI scores of 20-37 are typically classified as “no or low anxiety” (20-37), “moderate anxiety” for 38-44, and “high anxiety” for 45-80. (Marteau & Bekker, 1992) The Snaith-Hamilton Pleasure Scale (SHAPS) was also administered, offering an early understanding of anhedonia—the lack of pleasure in typically enjoyable activities—experienced by participants. The 14 items encompass various domains, including social interaction, food and drink, sensory experiences, and interest/pastimes. An individual is typically considered to have a "normal" score if it is 2 or less, while a score of 3 or more is categorised as "abnormal." (Snaith et al., 1995) Lastly, the Temporal Experience of Pleasure scale (TEPS) further enriched the initial evaluation, dissecting the anticipatory and consummatory aspects of reward and providing researchers with early insights into how participants anticipated and engaged with pleasurable experiences. Participants rate their response from 1 (very false for me) to 6 (very true for me) for 10 anticipatory and 8 consummatory items hence lower scores predict a higher proclivity to anhedonia. (Gard et al., 2006)

In conjunction with these psychological assessments, physical observations were also made at the beginning of the session. These encompassed monitoring vital signs, such as heart rate, blood pressure, respiratory rate, and temperature, as

well as measuring the participant's height and weight to calculate the BMI. Participants displaying bradycardia, with a pulse rate below 60, were excluded at this stage. Furthermore, the initial baseline taste-reward task was administered to eligible participants. This task is designed to investigate the rewarding aspects of taste perception. Later, either the drug or the placebo (an empty capsule) was dispensed to the participant. After waiting an hour for the drug to reach plasma peak levels, the participants were given computerised emotional and reward-processing tasks.

C. The Behavioural Tasks

The behavioural tasks conducted in the testing session can be distinctly categorised as reward-processing tasks and emotional-processing tasks.

Reward Processing Tasks

Two of the reward processing tasks (Probabilistic Instrumental Task and Effort Expenditure Task) involved incurring a further compensation based on their performance. The explanations given to participants are described below and the potential impact this might have had on the results is discussed in Part III.

- **Probabilistic Instrumental Learning Task**

All study participants undertook the Probabilistic Instrumental Learning Task (PILT) developed by Pessiglione et al. 2006. This task had two conditions involving either financial gains or losses, contingent on the particular pairing of two symbols rendered in the Agathodaimon font. Each symbol pair possessed its distinct set of probabilities governing the chances of winning or losing money. For example, one pair of symbols was associated with a notably high probability of yielding a financial gain. Opting for the correct symbol within this pair resulted in a £1 reward 70% of the time and a non-winning outcome 30% of the time. On the other

hand, selecting the incorrect symbol translated to a 70% chance of yielding no gain and a 30% likelihood of winning £1. Conversely, the other symbol pair was linked to financial losses. Here, the correct symbol selection prevented a loss in 70% of cases but, in 30% of situations, resulted in a £1 loss. Making an incorrect choice within this pair carried a 70% risk of incurring a £1 loss and a 30% chance of experiencing no loss. At the onset of the task, participants were given an initial sum of £3. Participants were informed that there symbols with higher likelihoods of winning and losing and that they were to be reimbursed according to their performance prior to starting the task. The task encompassed ten practice trials, succeeded by three experimental runs, each comprising 60 trials. Each run introduced a distinct set of four symbols. During every trial, one of the symbols from a pair was randomly displayed on the screen for 4,000 milliseconds. The symbol could appear either to the left or right of a centrally positioned fixation cross. Upon their selection, participants received instant feedback regarding the consequences of their choice. Their primary objective was to optimise their earnings by learning the connections between specific symbols and their associated outcomes as the trials progressed. The feedback served as a guiding principle for their subsequent choices, with the ultimate aim of selecting symbols linked to high-probability wins while avoiding symbols associated with high-probability losses. The outcome metrics encompassed various aspects, including the cumulative monetary value won, the net sum of both wins and losses, the frequency of specific choices, the percentage of consistency (the proportion of choices that mirrored the preceding selection), and reaction times.

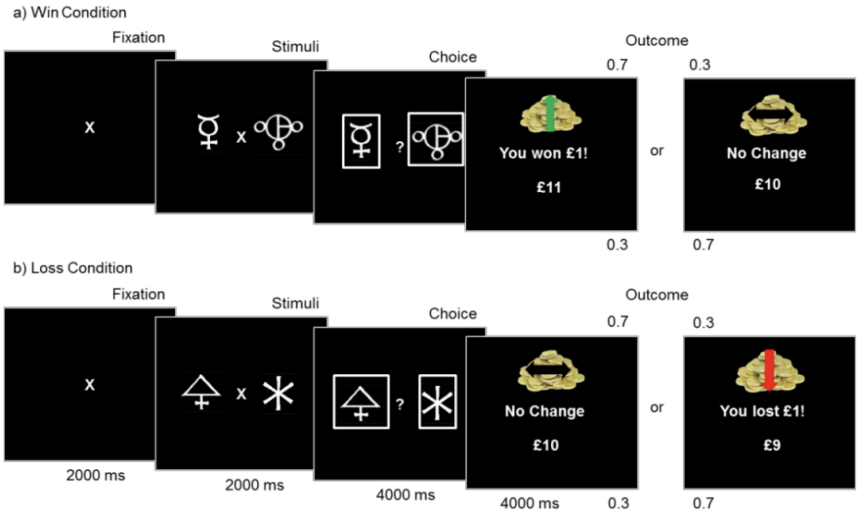

Figure 1: PILT: The test involved pairs of symbols associated with either a) winning or b) losing outcomes. The symbols represented a 70% or 30% probability for the associated monetary outcome. In each trial, a symbol from a pair was randomly presented on either side of a centrally placed fixation cross, serving as the focal point for participants. Immediate feedback followed each choice, guiding participants in maximising their monetary pay-offs.

- Taste-Reward Task

This task developed by Doherty et al. 2002 was conducted twice during the testing session, once before drug administration and the second time after. The time between the repetition of the tasks was approximately 2.5 hours for all. Before beginning the task, the participants were asked to select how much they predicted they would enjoy the sweet, sour, salty, and bitter tastes on a scale of -50 to 50. Then, the participants were asked to put four validated and standardised taste strips (sweet, sour, salty, bitter) into their mouths for 5-10 seconds and take them out afterwards. In the next 30 seconds, the participants were asked to rinse out/drink water to get the preceding taste out of their mouths and answer how much they enjoyed the taste (scale of -50 to 50) and how intense they believed the taste to be (scale of 0 to 100). The task was introduced after the first five participants, meaning the sample size was 17.

- Effort Expenditure Task

In this task developed by Treadway et al. in 2009, people were expected to raise a virtual bar by pressing a button repeatedly and received a reward if the bar reached the top. Participants chose between a hard task in which they had to press the button with their non-dominant little finger 98 times for the bar to reach the top in 21 seconds or an easy task where they had to press the button 30 times with their dominant index finger in 7 seconds. All participants had a fixed number of 57 trials. The potential monetary reward of each trial was shown on the screen and varied between 1.42 GBP to 4.12 GBP, conceptualised as *reward value* in the analysis; another information shown was the *probability level* of 'winning' the task, the three probabilities were 88%, 50%, and 12%. Even if the trial resulted in a successful completion of the task and then potentially was assessed as a 'win', only the results of two randomly selected trials (win or lose) were awarded to the participants. Participants were informed about the conditions for their compensation prior to starting the task in detail. The task was not conducted for the first five participants.

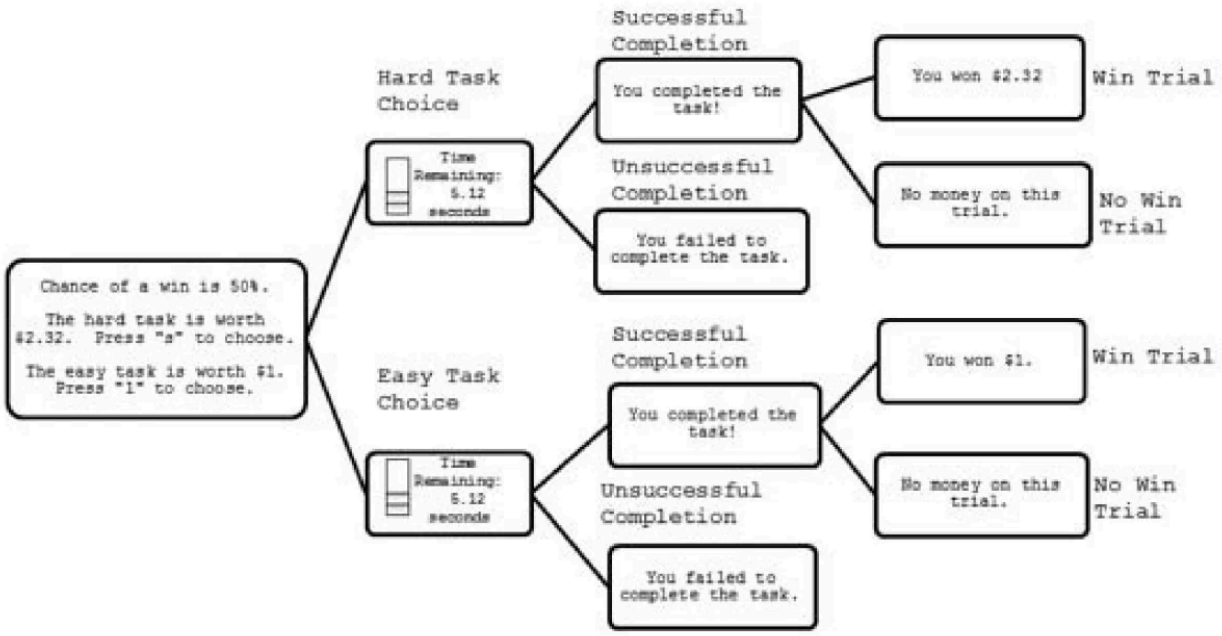

Figure 2: A demonstration of the steps of EEfRT. Firstly, the participant chooses the easy or hard version. Then, the participant either successfully completes or fails at the trial. If the participant has succeeded they can win money depending on the probability level.

➔ Divergence from the Traditional Version

Traditionally, the validated version of the task in MDD patients had a fixed time rather than a fixed number of trials. (Treadway et al., 2009) This resulted in measuring the strategy the participant developed in the face of an ambiguous optimal approach since there is no objectively correct method for winning more money. In that particular version, the data acquired from the task showed the computation of cost-benefit analysis as a whole rather than parsing the computation of effort in the face of different rewards. While this version of the task, fixed for trial number and not time, has been validated for ASD patients, there are other -similar- tasks that have shown a correlation between choosing to exert physical effort and

depression without any strategising. (Damiano et al., 2012; Cléry-Melin et al., 2011; Rizvi et al., 2016) In this version of the task, reward valuation and effort allocation are, in a way, dissociated from one another. Similarly, the data obtained gives way to other measures more linked with emotional processing. For example, the choice made by the participant after a 'loss' trial (either completed or uncompleted) can be interpreted as an appraisal of loss, which is more closely linked with emotional processing than a cognitive strategy developed as a response. Though, such an approach has its limitations, which will be further elaborated in Part III.

Emotional Processing Tasks

The three emotional processing tasks have all been adapted from the validated tasks of the Emotional Test Battery. (Harmer et al., 2004)

- FERT (Facial Recognition Task)

  The FERT assessed the interpretation of facial expressions. Faces with seven different basic emotions (happiness, fear, anger, disgust, sadness, surprise, neutral) were displayed on the screen for 500 ms and participants were required to indicate the expression on the face via a button press. Different intensity levels of each emotion were presented, which increased the ambiguity of the facial expression and the sensitivity of the task. Accuracy and speed were the main outcomes of this task.

- ECAT (Emotional Categorisation Task)

  The ECAT assessed speed and accuracy in responding to positive and negative self-referent personality descriptors. Forty personality characteristics (20 per valence) were selected to be disagreeable (e.g., sneering, untidy, hostile) or agreeable (e.g., cheerful, honest, optimistic) and were presented on a computer screen for 500 ms. The participants were asked whether they would like or dislike to be referred to as each characteristic promptly.

- EREC (Emotional Recall Task)

  The EREC was a surprise-free recall task to assess the incidental encoding of emotional stimuli. This task involved asking the subjects to recall as many words as possible from the ECAT task within 4 minutes. These two tasks allowed us to collect data on the storing, managing, and retrieving emotional information and the biases involved in these processes. This task was not computerised - participants wrote the recalled words on paper.

Order of The Tasks

1. FERT
2. ECAT
3. EFFORT EXPENDITURE TASK (EEfRT)
4. TASTE-REWARD TASK 2
5. EREC
6. PILT

The time between ECAT and EREC was 40 minutes (± 3 minutes) for all participants.

D. Protocol Deviations

The first 5 participants screened in person thus the baseline assessments were conducted during this visit. Secondly, the first five participants did not complete the EEfRT and the taste reward task. In the last 17 participants, only 1 participant deviated from the methodology described above. She did not complete the EEfRT and her FERT was not stored for technical reasons. This participant was administered the PILT in EEfRT's stead.

III. Results

A. Data Analysis Strategy

The sample size varied between 16 and 22 across tasks, and this low number significantly underpowered the study and the data accumulated. With this in mind, the strategy in the data analysis was to approach the data in a more exploratory manner than a methodological one. The alpha level for statistical significance was capped at 0.10; these results were identified as indicating a *trend*. The first instance across all analyses was two-way ANOVA testing, apart from the Probabilistic Instrumental Learning Task, because all tasks had at least two factors with a presumed effect on the dependent variable. If there was a significant difference between the variations, the conservative Greenhouse-Geisser correction was used to address violations of sphericity. Most of the ANOVA results yielded high sums of squares for residuals, so even if no significant result was found in the ANOVA, the factors were examined individually with t-tests, and Welch's two-sample t-tests were used to account for different standard deviations. Overall, potential factors that were presumed to affect the data were addressed individually, even if ANOVA returned no statistical significance.

B. Questionnaire Data

Table 1 shows statistics from questionnaire data of the last 17 participants. 1 of the participants in the Placebo group scored 15 on the BDI.

	TEPS-ANT (means±SD)	TEPS-CONS (means±SD)	BDI (means±SD)	SHAPS (means±SD)	PANAS-P (means±SD)	PANAS-N (means±SD)	STAI-S (means±SD)	STAI-T (means±SD)	EPQ-N (means±SD)	EPQ-P (means±SD)	EPQ-L (means±SD)
selegiline	45.8 ± 6.8	39.8 ± 5.0	1.8 ± 1.5	1±2.1	36.4±5.0	11.5±1.4	25.9±5.3	28.2±4.1	2.7±2.2	2.9±2.3	9.2±3.3
placebo	45.1±4.5	39.1±3.8	2.7±5	0.7±1.2	30.7±7.4	12.6±1.8	30.4±6.3	34.9±7.6	7.7±6.6	3.4±3.6	8.6±4.1

Table 1: The statistics of the Questionnaire Data of each group from the last 17 participants.

The t-tests of the values from Table 1 showed no statistical significance regarding the effect of the medication group on the results, though STAI-T ($p = 0.08$) was noteworthy. Placebo has a trend of higher trait anxiety, whereas the other results are not statistically significant.

C. Reward Processing Tasks

- ### Taste-Reward Task (n=17)

A two-way ANOVA analysis was conducted, considering all the factors, including taste, medication group, response rating, and response type, along with their interactions. The results revealed that taste ($F(7, 15) = 30.1$, $p < 0.001$), response type ($F(2, 15) = 72.9$, $p < 0.001$), and the interaction between taste and response type ($F(14, 15) = 12.8$, $p < 0.001$) were all statistically significant factors affecting the variation in response ratings. However, the medication group had no overall impact on the dependent variable ($F(1, 15) = 0.082$, $p = 0.779$). The three-way interaction involving medication group, response type, and taste was also not significant ($F(14, 15) = 0.395$, p-value = 0.976). Notably, the sum of squares for the residuals was calculated to be 107485.

Figure 1 shows the change in ratings between the first and the second administration of the taste reward tasks as the dependent variable. There does appear to be a trend for the selegiline group to have lower reductions in anticipation of each taste. The exception is the bitter taste, which regularly showed a different direction than other tastes.

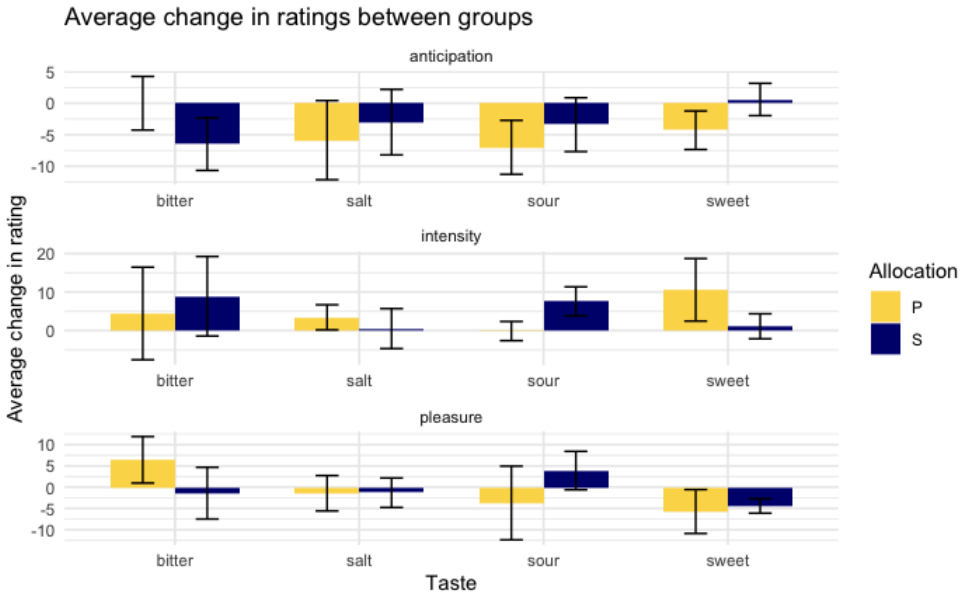

Figure 1: Differences in baseline and testing session values categorised by response and taste types. P stands for Placebo, and S stands for selegiline.

In order to assess that individually, a two-way ANOVA was conducted on the anticipation data, this also revealed no significant result for the medication group. ($F(1, 15) = 0.494$, $p = 0.493$). There also appeared to be no significant interaction between the medication group and taste regarding the response type Anticipation response change. ($F(3, 15) = 1.01$, $p = 0.398$) The overall sum of squares was once again high, 15,498 for within-subject analysis and 6430 for the medication group.

Individual Welch t-tests between placebo and selegiline in the anticipation response type across tastes showed notable results. The most significant result was in the anticipation of the sweet taste. (S M = 0.60, P M = -4.29; $p = 0.084$) This analysis reveals a noticeable trend in the selegiline group, indicating a milder reduction in anticipation value than the control group. It is possible that the placebo group started with exceptionally high anticipation and subsequently regressed to the mean, while the selegiline group remained stable; to account for this, baseline anticipation levels should have been measured and

included in the analysis. The only increase in the reduction of anticipation for selegiline was observed for the bitter taste, though this was not significant (P M = 0.0, S M = -6.50; p-value = 0.121). The effects of selegiline on the anticipation of sour and salt tastes were negligible. (P M = -7.0, S M = -3.4; p = 0.391)

Despite, the intensity response type of the sour taste appearing significant in the figure, the Welch t-test showed no significant results, with the selegiline group reporting higher intensity (P M = -0.143, S M = 7.60; p = 0.105). The difference in intensity of the sweet taste showed an opposing, though once again insignificant, result with the selegiline group reporting lower intensity. (P M = 10.5, S M = 1.10; p = 0.130).

- Effort Expenditure Task (n = 16)

The participant with the BDI = 15 was excluded from this task due to technical reasons thus the sample size was 16. The data analysis strategy for the EEfRT was to filter when a hard trial was chosen. Then, this number was divided by 57 (trial number) to obtain the proportion of hard choices. The Welch t-test that compared the two groups showed that the proportion of hard choices was numerically lower for selegiline than placebo, though not significantly. (P M = 0.401, S M = 0.311; p = 0.293)

In order to assess how probability levels might have impacted the proportion, a two-way ANOVA with the medication group and probability levels as factors was conducted. While the medication group's effect was negligible ($F(1, 14) = 0.806$, $p = 0.374$), the probability level played a significant role in the variation of the results. ($F(2, 14) = 33.0$, p-value<0.001)

The interaction between the medication group and probability level was also not significant. ($F(2, 14) = 0.540$, p-value = 0.59)

The rewards ranging from 1.42 to 4.12 were binned into three groups: small, medium, and large. Small was defined as 1.42 to 2.32 (not included), medium as 2.32 to 3.22 (not included), and large was defined as 3.22 to 4.12. A two-way ANOVA testing of the reward category and medication group showed that only the reward category impacted the results. ($F(2, 14) = 28.5$, $p < 0.001$) The medication group individually and the interaction between the medication group and reward category had no significant result. ($F(1, 14) = 0.946$, $p = 0.336$; $F(2, 14) = 0.038$, $p = 0.963$)

Individual t-tests across reward categories were conducted. None of them showed any significant results. For small rewards, S M = 2.20, P M = 3.00, and $p = 0.487$. Meanwhile, for medium rewards, S M = 6.00, P M = 6.67, and $p = 0.663$. Finally, for big rewards, S M = 10.4, P M = 11.7, and $p = 0.532$.

- Probabilistic Incentive Learning Task (n = 21)

A participant's PILT data was excluded from the analysis because they did not complete two-thirds of the task. To begin with, a Welch Two Sample t-test was applied to the total amount won by each Medication Group. (P M = 5.88, S M = 5.28; $p = 0.532$). The results indicate that there was no significant difference between the mean amounts won by placebo and selegiline.

In order to assess the amount won in the three runs of PILT separately, the t-tests were performed individually for each block. In Block 1, the Welch Two Sample t-test yielded no significant difference in mean amounts won. (P M = 1.84, S M = 2.00; $p = 0.699$) In Block 2, a similar Welch Two Sample t-test was performed, and it was found that there was no significant difference in the

mean amounts won by the two groups. (P M = 2.32, S M = 1.84; p = 0.333) In Block 3, the same Welch Two Sample t-test yielded no significant difference between the mean amounts won by the two groups (P M = 1.72, S M = 1.44; p = 0.599).

Beyond the amount won, the analysis also included the difference in the proportion of high-probability symbols chosen in win and loss trials. The Wins Proportion test showed no statistical significance (P M = 78.00; S M = 69.44; p = 0.381). Similarly, the Loss Proportion test yielded no statistical significance (P M = 66.00, S M = 70.88; p = 0.466). All participants learned the high-probability stimuli after the first 10 trials.

Further analysis was conducted on the proportions of wins and losses in Blocks 1, 2, and 3. Welch Two Sample t-tests were performed for all three blocks, and no significant differences were found in the proportions of high probability symbols chosen in win and loss trials between the two groups. (Win Block 1: P M = 78.33, S M = 73.67, p = 0.733; Win Block 2: P M = 85.00, S M = 74.33, p = 0.371; Win Block 3: P M = 70.67, S M = 60.33, p = 0.556; Losses Block 1: P M = 60.33, S M = 76.67, p = 0.1013; Losses Block 2: P M = 68.33, S M = 68.67, p = 0.9686; Losses Block 3: P M = 69.33, S M = 67.33, p = 0.7958)

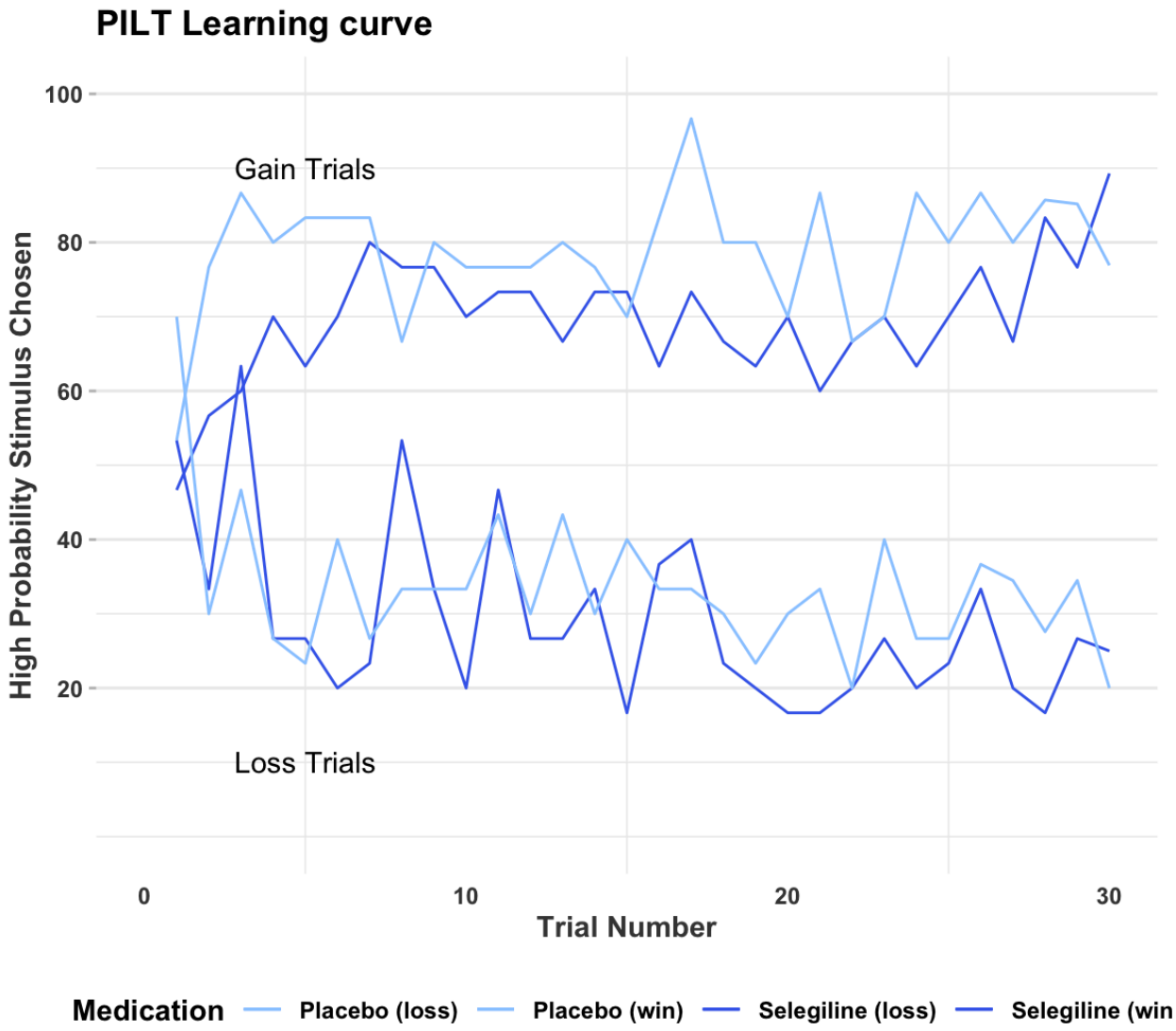

Figure 3: The learning curves visually represent the temporal evolution of gain and loss trials within both experimental groups, where the y-axis denotes the proportion of selections favouring the high probability stimulus, and the x-axis signifies the sequential trial number. Thus, the curves represent the proportion of runs in which a participant chose the advantageous shape, i.e., the shape linked to a 70% likelihood of achieving a win outcome or no loss outcome in a given trial.

A graph of both groups' learning curves for loss and win trials. The learning curve of win trials in placebo appeared more asymptotic than selegiline's learning curve. In order to assess whether the lines were significantly

different from one another, exact two-sample Kolmogorov-Smirnov tests were conducted for win and loss lines for the two medication groups. For win lines, there was a statistically significant result. ($D = 0.567$, $p < 0.001$) The test for loss lines also revealed a significant difference between the datasets. ($D = 0.4$, $p = 0.008$). This showed that the lines were statistically supported to belong to different populations.

The observed curves indicate that all participants learned the task after the 10th trial. Subsequently, Welch's t-test was performed on both win and loss trials, encompassing data from the 10th trial onward, and involving the two medication groups and aligned with signal detection theory, post-learning task data yields reward sensitivity—a measure of participants' propensity to alter behaviour in response to rewards. The analysis concluded that the selegiline group showed statistically significant lower reward sensitivity for both win and loss trials. (Win: P M = 79.724, S M = 70.964, p-value = 0.0004; Loss: P M = 31.828, S M = 25.750, p-value = 0.017)

In conclusion, the comprehensive analysis of the statistical tests conducted on the impact of medication on PILT outcomes demonstrates that there were no significant differences in terms of total amount won, proportions of wins and losses, or their variations across different blocks between placebo and selegiline. However, the difference between reward sensitivity in both win and loss trials is significant, showing that the placebo group is more sensitive.

D. Emotional Processing Tasks

- FERT (n = 21)

The participant with the BDI = 15 was excluded from this task due to technical reasons. For accuracy, a two-way ANOVA that factored in medication group and emotions on accuracy rate was conducted. The medication group's effect was insignificant. ($F(1, 19) = 1.281$; $p = 0.272$) The interaction between the medication group and emotion was also insignificant. ($F(6, 19) = 0.842$; $p = 0.54$) On the other hand, emotion had a significant impact on the data. ($F(6, 19) = 93.077$; $p < 0.001$)

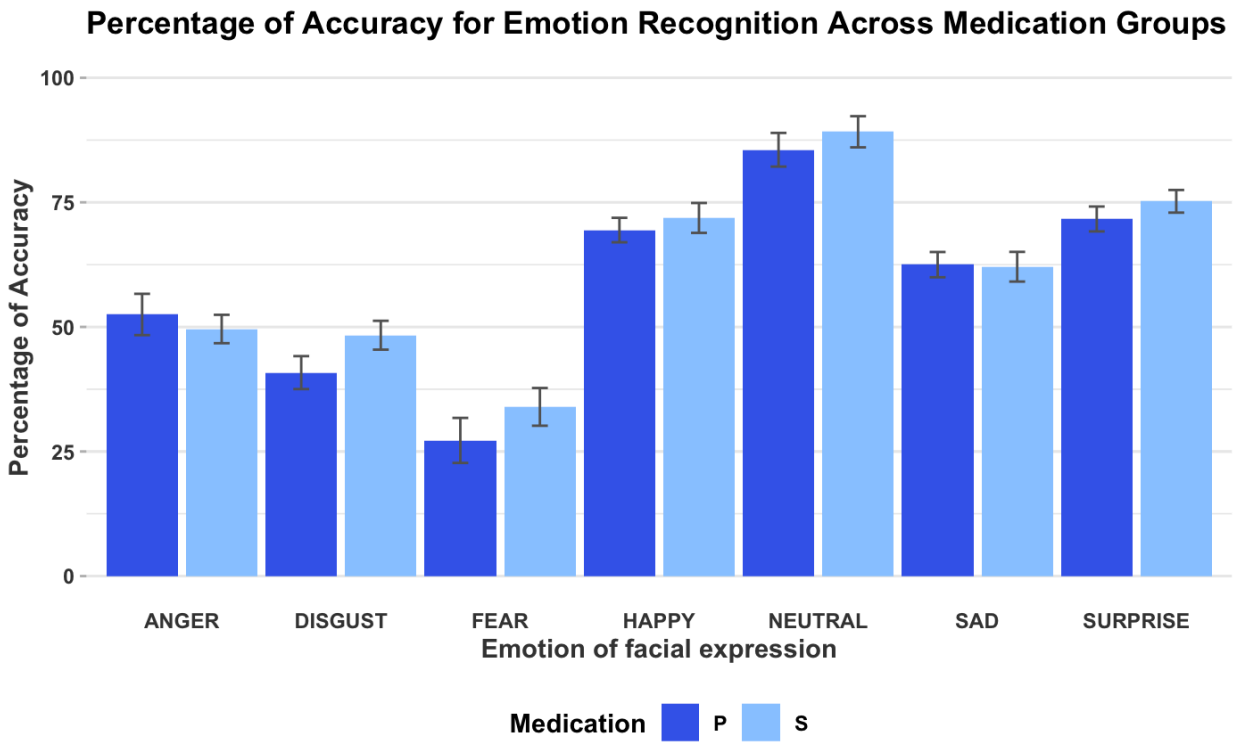

Figure 4: The depicted data illustrates the accuracy percentages in emotion recognition across distinct medication groups categorised by different emotions. In this context, "P" designates the placebo group, and "S" signifies the selegiline group.

Given the effect of emotion as a significant factor on the results, post-hoc analyses of separate emotions were conducted. In Figure Y, there seems to be an increase in the accuracy percentage in the selegiline for disgust. However, a Welch's t-test did not produce significant results for increased accuracy in identifying disgust in the selegiline group. (P M = 40.833, S M = 48.333; p = 0.106) Another emotion that the graph showed a potential difference for was fear. However, yet again, the Welch's t-test did not yield any statistically significant results. (P M = 27.222, S M = 33.958; p = 0.269)

In order to see if the accuracy was driven at all by a better performance of distinguishing between faces, a signal detection analysis was conducted through the unbiased hit rate (UBHR). The UBHR is calculated by utilising a specific emotion's hit rate (accurate press rate) and the false alarm rate (inaccurate press rate).

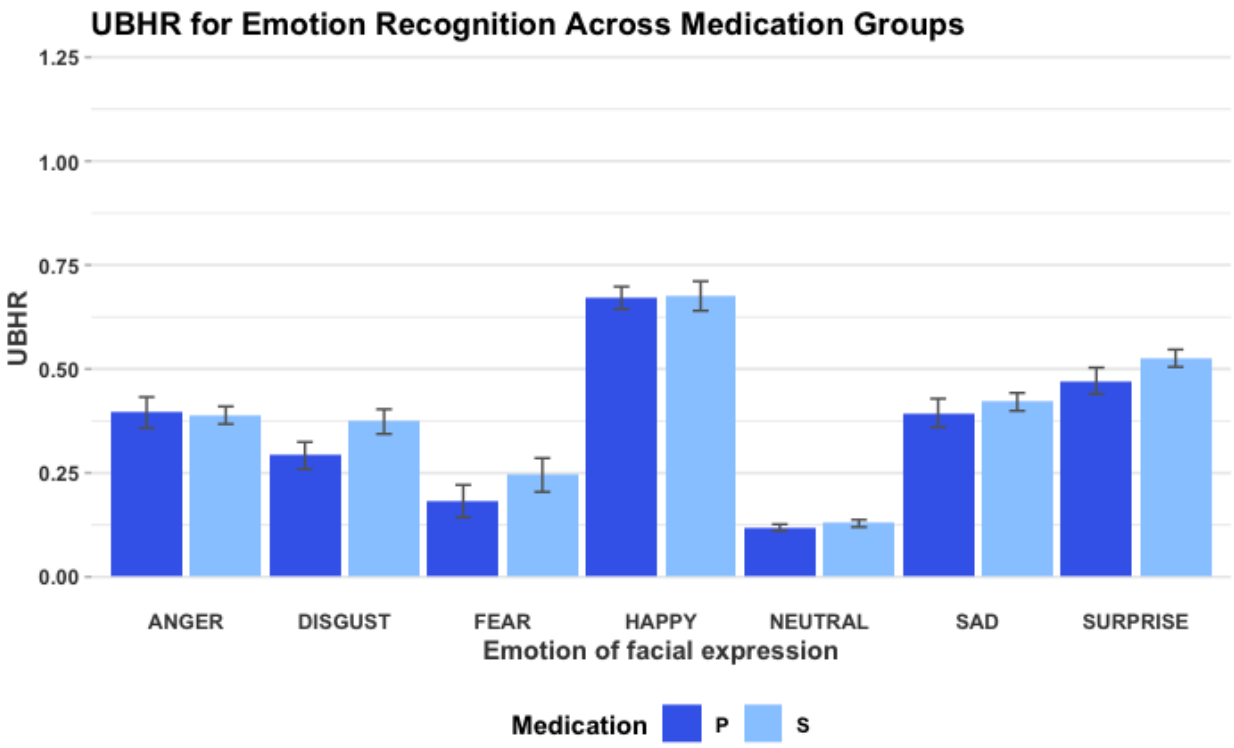

Figure 5: The provided data highlights the unbiased hit rate (UBHR) in emotion recognition across distinct medication groups categorised by different emotions. The

UBHR is computed using signal detection theory. "P" represents the placebo group, and "S" signifies the selegiline group.

ANOVA of UBHR that factored in emotion categories and medication group and their interaction showed no significant results, excluding emotion categories. (*Medication group:* $F(1, 19) = 1.357$, $p = 0.258$; *Emotion:* $F(6, 19) = 124.258$, $p < 0.001$; *Interaction:* $F(6, 19) = 1.034$, $p = 0.407$) Post-hoc analyses of individual emotions with Welch's t-test were limited to disgust, which showed a statistically significant difference in accuracy. Once again, there was an upward trend for identifying disgust in the selegiline group. (P M = 0.292, S M = 0.373; $p = 0.081$)

Subsequently, an exploratory analysis of misclassifications (false alarms) was conducted. The ANOVA results for misclassifications of emotions show that the main effect of the medication group is statistically non-significant. ($F(1, 19) = 2.488$; $p = 0.133$). However, there is a marginally significant interaction between the medication group and emotion categories ($F(6, 19) = 3.210$; $p = 0.091$), suggesting a potential trend where the combination of specific medications and emotions may have some effect on misclassification. A significant main effect of emotion categories is also observed ($F(6, 19) = 113.749$; $p < 0.001$), indicating that different emotions significantly influence misclassification rates. These findings suggest that while emotions substantially impact misclassification, medication groups and their interaction with emotions might also account for the variation in the data.

A post-hoc analysis of emotions that appeared potentially different in Figure Z was conducted. In the analysis of misclassifications for anger, a Welch's t-test shows that the main effect of the medication group is not statistically significant (P M = 7.333, S M = 5.750; $p = 0.343$). This suggests that different medication groups do not significantly affect misclassifications for angry emotions. The residuals (sum of squares = 19230 and 19369)

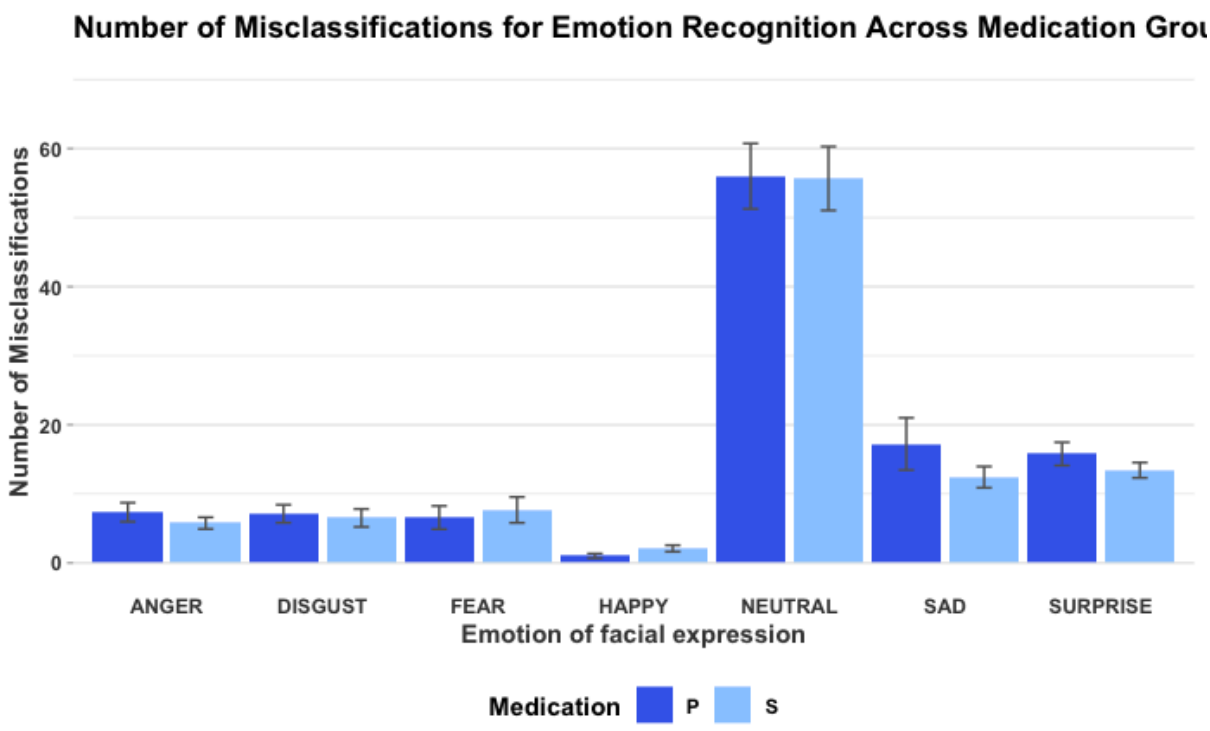

Figure 6: The provided data illustrates the number of misclassifications in emotion recognition across distinct medication groups, categorised by different emotions. "P" designates the placebo group, and "S" signifies the selegiline group.

account for much of the variance. However, there is an upward trend in the misclassifications of happy emotions in the selegiline group. (P M = 1.000, S M = 2.083; p = 0.075). Lastly, a Welch Two-Sample t-test is used to compare the two medication groups in the misclassification of sad faces. There was no statistically significant difference. (P M = 17.222, S M = 12.417; p = 0.265).

The final parameter assessed was reaction time. ANOVA that factored in emotions, medication group and their interaction was conducted. Only emotion categories yielded a significant effect. (*Medication group:* $F(1, 19) = 0.115$, $p = 0.739$; *Emotion:* $F(6, 19) = 17.18$, $p < 0.001$; *Interaction:* $F(6, 19) = 0.35$, $p = 0.909$) The sum of squares of the residuals for this analysis was 8643918, meaning the model did not fully capture the data and was noisy.

- ECAT (n = 22)

Firstly, a two-way ANOVA was performed with the factors medication group and valence on "Correct Responses." In this analysis, the effect of the medication group showed no statistical significance ($F(1, 20) = 0.31$, $p = 0.587$), indicating that different medication groups did not significantly impact correct responses. Similarly, the effect of valence was not statistically significant ($F(1, 20) = 1.866$, $p = 0.195$). The interaction effect between these factors was also not significant ($F(1, 20) = 1.754$, $p = 0.208$). Similarly, for "Incorrect Responses," the ANOVA analysis showed no statistical significance for the effect of "Medication Group" ($F(1, 20) = 0.31$, $p = 0.587$), indicating that different medication groups did not significantly affect incorrect responses. In contrast, the effect of valence was not statistically significant ($F(1, 20) = 1.866$, $p = 0.195$), signifying that valence had an effect on incorrect responses. However, the interaction effect was not statistically significant ($F(1, 20) = 1.754$, $p = 0.208$).

Secondly, the variation in reaction time was analysed similarly to the other outcome. First, a two-way ANOVA was conducted and yielded no statistically significant result for the medication group, valence, or their interaction. ($F < 1.62$, $p > 0.216$) The sum of squares of the residuals was 1502823. Then, exploratory Welch t-tests were separately executed for positively and negatively valenced words. Neither rendered statistically significant results for the difference between placebo and selegiline, though selegiline had lower means in both. (*Positive*: P M = 1001.28, S M = 908.69, $p = 0.495$; *Negative*: P M = 1141.96, S M = 1024.87, $p = 0.475$)

- EREC (n = 22)

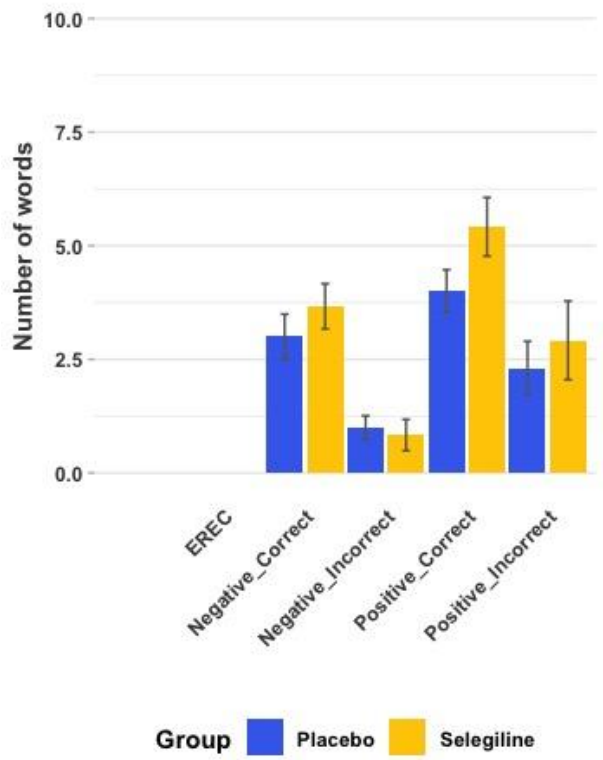

Figure 7: The results of the EREC are categorised by the valence and accuracy of the words recalled. Blue represents the Placebo Group, and Yellow represents the selegiline Group.

The results of this task were analysed using both Greenhouse-Geiser corrected ANOVA (since sphericity was violated) and t-test analyses. In the Greenhouse-Geisser corrected ANOVA analysis, neither the main effect of the medication group nor the interaction between the medication group and the category was statistically significant for both correct and incorrect responses.

Subsequently, exploratory t-tests were performed to assess specific response categories. For "Positive Incorrect" responses, a two-sample t-test revealed no significant difference in means between group P and group S (P M = 2.72, P SD = 1.48, S M = 2.85, S SD = 2.87; p = 0.5799). Meanwhile, for

"Positive Correct" responses, the Welch two-sample t-test (P M = 4.09, P SD = 1.41, S M = 5.31, S SD = 2.14; p = 0.092) indicated a discernible upward trend in the recall of Positive Correct responses within the selegiline group.

For "Negative Correct" responses, a Welch two-sample t-test showed no significant difference in means (P M = 3.10, P SD = 1.48, S M = 3.77, S SD = 1.65; p = 0.3533). Lastly, for "Negative Incorrect" responses, a Welch two-sample t-test (P M = 0.91, P SD = 0.77, S M = 0.77, S SD = 1.14; p = 0.7029) revealed no significant difference in means between group P and group S.

E. Concluding Remarks

For the reward tasks, the data appears to follow different directions. In the context of taste reward, both sweet and bitter tastes exhibited a more pronounced impact on the difference between baseline and testing responses. There was a coherent reduction in anticipation ratings in the selegiline group, excluding the bitter taste, which showed, in fact, an increased lowering of the anticipation rating. The sweet taste was the only anticipation rating that showed statistical significance in the subsequent t-tests. The experience of the intensity levels of sour was also affected by the medication group, though it was not significant. However, it's important to note that the data exhibited significant noise, which can complicate interpretations. In the PILT task, the graph shows a less asymptotic curve for selegiline compared to placebo and a lower stabilised value for both reward and loss, which implied delayed and reduced acquisition of reward bias. The reduced reward bias is supported by

statistical analysis. Finally, no significant results were observed for the EEfRT task.

The results of the emotional processing tasks were incoherent as well. In the FERT task, the emotion category was found to significantly impact the data. Participants in the selegiline group also displayed a greater tendency to misidentify emotions as happy when they were not. In the ECAT task, the results suggest that the medication group and valence factors had limited to no influence on the task's outcomes. Meanwhile, for the EREC task, the ANOVA results indicate that valence significantly influenced both correct and incorrect responses. Subsequent t-tests for specific response categories indicated that selegiline increased the recall of Positive Correct responses. The graph seemed to suggest an overall increase in performance for the selegiline group. Still, this observation was not supported by the analysis, possibly due to the high standard deviation in all categories for both groups, indicating the need for a larger sample size.

The noise observed with standard deviations and the residuals overarchingly suggests further exploration with a larger sample size is required to make conclusive statements about the results.

PART III:

Conclusion: Discussion of Findings, Study Limitations, and Future Directions

A. Main Results of Study

In examining reward tasks, diverse trends emerge within the dataset. Taste reward, specifically sweet and bitter stimuli, exerts a noticeable impact on the distinction between baseline and testing responses. The selegiline group exhibits a coherent reduction in anticipation ratings, except for the bitter taste, where an increased lowering of anticipation ratings is observed. The sole anticipation rating achieving statistical significance pertains to the sweet taste. Furthermore, the perception of sour intensity initially appeared to be significantly affected in the graph. However, statistical analysis showed it was insignificant. It is crucial to note the substantial noise in the data, posing challenges to unequivocal interpretations. The Probabilistic Instrumental Learning Task (PILT) reveals a less asymptotic curve for selegiline compared to the placebo in both reward and loss trials, indicating delayed and reduced acquisition of reward bias. The later statistical analysis also concluded that reward bias was reduced significantly for the selegiline group in both win and loss trials.

Moving to emotional processing tasks, the Evaluation of Emotional Faces task (FERT) presents incongruent outcomes. The emotion category significantly impacts the data. Participants in the selegiline cohort also exhibit a heightened propensity to misidentify non-happy emotions as happy. Shifting to the Emotional Categorization and Appraisal of Threat (ECAT) task, the results imply limited to no influence from the medication group and valence factors on task outcomes. Conversely, the Emotional Recognition (EREC) task reveals that valence significantly affects both correct and incorrect responses. Subsequent t-tests for specific response categories indicate an increase in the recall of Positive Correct responses with selegiline. Although the graphical representation suggests an overall performance enhancement in the selegiline group, this observation lacks statistical support, possibly owing to elevated standard deviations in all categories for both groups, underscoring the necessity for a more extensive sample size.

B. Interpretation of Results

It is important to reiterate that the sample size varied between 16 and 22 across tasks, and this low number significantly underpowered the study and the data accumulated.

a. Reward Tasks

As discussed, there appears to be some preliminary evidence that the anticipation of reward was better preserved for the selegiline group apart from the bitter taste. While only the sweet taste demonstrated statistical significance at the 0.1 threshold, the upward trend in the selegiline group's graph is promising, pointing towards potential insights with a larger sample size. Regardless, the main finding of this task is the reduction in the lowering anticipation of the sweet taste. These results align with the predicted outcomes discussed in the introduction, demonstrating that dopamine induces a favourable shift in the anticipation—specifically, in the 'wanting' aspect of reward. Furthermore, the wanting aspect in this task is not fully distinguished from the learning component of reward. While the participants are not under any medication or placebo while they experience the tastes for the first time, they are ‘recalling’ a specific learned experience when anticipating. Arguably, learning from the baseline session is not temporally distinct from the anticipation phase. Another caveat to note is that there is a possibility that the placebo group initially had exceptionally high anticipation, leading to regression to the mean, while the selegiline group remained stable. This would mean the main difference lies with the baseline anticipation rather than its preservation, which would potentially mean the opposite of our argument: selegiline *lowers* anticipation. On the other hand, performing the task twice and analysing the difference reduces the impact of individual differences on the data.

Another noteworthy observation is the valenced nature of reward processing as conceptualised by this task. The opposite trend was observed in

the bitter taste compared to the other three. Our main finding related to the only positively valenced taste: sweet. Thus, once the study is replicated with a bigger sample size, we could better understand whether the bitter taste, the only objectively negative taste, follows a contrarian trend for the selegiline group. This would mean that although dopamine is involved in the computation of both valences, the effects of MAO-B inhibition differentially affect the two. This could be related to a multitude of factors, not excluding MAO-B placement, different algorithms used for different valences, etc.

In contrast, selegiline's effects on other aspects of reward in this task are less apparent. Neither pleasure nor intensity appeared to be affected apart from the intensity of the sour taste. While it did not pass the 0.1 threshold, it could potentially be noteworthy with a larger sample size. Alternative explanations could be related to when the participants ate or individual preferences for the sour taste. The small sample size could be augmenting the effects of these confounding factors. Otherwise, MAO-B inhibition could be impacting gustatory computations.

Conversely, the selegiline group exhibited markedly negative results in processing reward during the probabilistic instrumental learning task. The learning curves showed a delayed and blunted response to both reward and loss. Interestingly, these results partially echo those of acute experiments with bupropion and pramipexole that employed the same task. (Walsh et al., 2018; Pizzagalli et al., 2008) In the bupropion and pramipexole experiments, there was a blunted response to reward, but not to loss, in the medication group. (Walsh et al., 2018; Pizzagalli et al., 2008) An explanation of both results relied on rodent studies that showcased the possibility of these drugs culminating in acutely low levels of striatal dopamine. (Walsh et al., 2018; Pizzagalli et al., 2008; Voon et al., 2017) Both bupropion and pramipexole can bind to the dopamine autoreceptors to downregulate dopamine synthesis in the presynaptic neuron, decreasing the synaptic dopamine concentrations. (Voon et al., 2017; Ito et al., 2000; Weiss et al., 2000)

However, as discussed in Part I-Chapter V, selegiline purportedly *inhibits* dopamine autoreceptors, further increasing the synaptic dopamine. (Heinonen et al., 1994; Knoll, 1979) Thus, the findings from the other two studies may not explain these results. Though, selegiline's acute neurophysiological effects are still not fully understood. Selegiline's pharmacokinetics and functionality have been predominantly tested for PD. Still, research has underutilised current technological advances to investigate whether selegiline acutely increases or decreases dopamine levels and to identify the specific anatomical structures in which it is more effective. Likewise, the biochemical interaction between selegiline and the dopamine autoreceptors is under-researched, especially acutely. While the claim of autoreceptor inhibition can be found in the literature, there does not appear to be clear and rigorous evidence of autoreceptor inhibition and reads more as a supposition.

Similarly, as an MAO-B inhibitor, selegiline could inhibit the oxidation of other neurotransmitters, more relevantly serotonin. As discussed in the introduction, the findings show dopamine is far more affected than serotonin. However, this does not mean there is also no functional increase in serotonin. Once again, our limited understanding of selegiline's neurophysiological effects impedes us from formulating definitive explanations of the behavioural data. The conclusion that serotonin is not as affected relies on the data gathered from autopsies of PD patients with small sample sizes and the concentrations in the plasma levels. As such, it is difficult to determine the exact effects of selegiline on serotonin levels of healthy brains and whether the minute differences that could be disregarded about PD could be functionally significant in these acute behavioural tasks. Interestingly, these findings echo the research on serotonergic medication, which has found negative effects on reward processing and its neural correlates. (Macoveanu et al., 2014; McCabe et al., 2010).

L-Dopa or levodopa and l-3,4-dihydroxyphenylalanine, another dopaminergic medication, has also been investigated for its effects on reward. L-dopa, a precursor for dopamine, globally increases the amount of dopamine in the brain and, as a result, in the synapses. Given that the neurophysiological effects of l-dopa and selegiline are potentially closer than those of agonists and reuptake inhibitors, the research on l-dopa carries tremendous weight. Repeatedly, research with l-dopa predicts worse outcomes with tasks that involve reinforcement learning. (Shohamy et al., 2006; Vo et al., 2016) In fact, aberrant salience attribution and reduced performance in reinforcement learning behavioural tasks correlated positively with ventral striatal presynaptic dopamine levels measured in healthy individuals' areas activated by RPEs (reward prediction errors). (Boehme et al., 2015) Possibly, increasing dopamine impedes the temporally sensitive nature of salience attribution. There could be a multitude of mechanisms explaining why the interference with the dopaminergic circuitry consistently yields lower performance with tasks relating to reward learning: (1) as discussed above, the premature inhibition of the autoreceptors could explain lower phasic firing, (2) increase in dopamine levels in the striatum could incorrectly activate the D1 or D2 pathways given how concentration-sensitive these pathways are, (3) increasing tonic dopamine levels could decrease the dynamic range, salience, and detectability of phasic dopamine signals (Shohamy et al., 2006; Vo et al., 2016) Dopamine is highly implicated in the credit assignment algorithm in reward processing, and this is a highly temporally regulated process. (Stuber et al., 2005; Schultz, 2007) Thus, artificially interfering with the dopaminergic circuitry especially acutely impedes this computation.

While the analysis of PILT purportedly shows how likely the participant is affected by reward, i.e. reward sensitivity, it is worth noting that the learning process carries on during the task. The unvalenced nature of the decreased performance of the selegiline group does raise the question of whether this is a result of aberrant reinforcement learning rather than sensitivity. Levodopa

research has also found impaired reward and punishment-based learning. (Vo et al., 2016) In fact, the detrimental effects of l-dopa on task performances are limited to the learning components but not the transfer of knowledge. (Shohamy et al., 2006) Similarly, dopamine "overdose" has been hypothesised to impair feedback-based learning that relies on temporally specific, stimulus-specific information but not task-switching ability, generalisability, and sequence learning. (Cools et al., 2001; Shohamy et al., 2006) Treatments with dopamine agonists have been found to impair reward learning as well. (Pizzagalli, 2008)

Overall, there are many potential explanations for the Probabilistic Instrumental Learning Task results. In order to propose a neurocognitive framework for these findings, pharmacological research that utilises more recent technologies, i.e. PET, is imperative. It is also important that this research is conducted on humans or animals with a similar MAO-B distribution in the brain. Though given the similarity of our findings and other dopaminergic medication, the most plausible explanation is possibly the credit assignment impairment caused by interference with the midbrain dopaminergic system. Importantly, this is supported by the detrimental effects on both win and loss trials, which are not replicated in similar bupropion and pramipexole studies. Tasks that distinguish reward sensitivity and reward learning could paint us a more accurate picture. Moreover, employing such a task could enhance the predictive validity of how the medication influences reward processing in real-life scenarios. This is particularly significant, as real-life rewards may exhibit a different level of sensitivity due to the absence of stringent temporal encoding requirements.

Furthermore, while the acute results of PILT provide a grim picture of how selegiline and dopaminergic medication affect reward processing, the subacute and longitudinal research challenges this notion. Potentially, homeostatic processes down-regulate the initial confusion caused by the acute interference with the dopaminergic system. Both pramipexole and bupropion

have found better performance at PILT than placebo after subacute treatment. (Halahakoon et al., 2023; Walsh et al., 2018) They have also seen more activation in regions related to reward processing in fMRI studies. (Halahakoon et al., 2023; Ikeda et al., 2019) These findings are similar to research with SSRIs. (Macoveanu et al., 2014; McCabe et al., 2010)

In the Effort Expenditure Task, we found that selegiline had no effect on the decision-making relating to effort. Apart from the statistical reasons discussed in D, which is more relevant for this task as it has the lowest sample size, there could be other reasons for task design. For one, the divergence from the original version of the task might be the reason for the null findings. This would mean that the abstraction of reward and effort caused by a lack of optimal strategy could have been the more crucial aspect regulated by dopamine. Individual differences in dopamine (DA) function in the left striatum and ventromedial prefrontal cortex correlated with a greater willingness to expend effort for larger rewards, especially when reward probability was low, with the original version of the EEfRT. (Treadway et al., 2012) However, there are other tasks that investigate effort and depression that are similar in their straightforwardness. The majority of studies have indicated that in the context of depression, there is a reduction in the willingness to exert effort rather than a diminished engagement in cost/benefit strategising. (Halahakoon et al., 2020) Secondly, the reason for the null findings could be the reward itself. The amount of money promised could have been deemed too little, or the difference between high and low reward value could have been too minimal.

When interpreting the results of the reward tasks, it is fruitful to try and integrate them in the hopes of a unified picture. Though this enterprise comes with certain limitations as discussed in D, and also due to the differences in the tasks in conceptualising and demarcating reward itself and its components. The taste reward task utilises a primary reward, whereas the other two reward tasks employ a secondary one. The dopaminergic system is

indeed found to be differentially implicated in these two types of rewards. (Stuber et al., 2008) Similarly, valence would be computed differently in the primary and secondary types of reward since one involves conditioning while the other involves a more evolutionarily conserved and delineated structure. Overarchingly, while piecing together this puzzle remains valuable, it does come with certain caveats, mainly with how reward is interpreted as a concept.

Nonetheless, despite these caveats, selegiline appears to have opposing effects on the different components of reward. While it positively impacted anticipation, it reduced reward sensitivity. An experiment with the Monetary Incentive Delay Task could tell us a more unified interpretation since it would utilise the same type of reward -money- for both anticipation and reward sensitivity.

b. Emotional tasks

For the emotional tasks, we observe a more consistent portrait of selegiline's impact. While this may be attributed to the statistical shortcomings of the current sample size, as discussed in D, it could also just indicate that selegiline positively impacts emotional processing. In FERT, there is a potentially insignificant increase in accuracy and sensitivity when categorising disgust. This could preliminarily indicate heightened processing of negatively valenced emotions. However, since disgust is the sole emotion affected and other negatively valenced emotions remain unchanged, this alteration might be attributed to other specific reasons related to disgust. Anger, in particular, appears to be lowered, though not significantly.

For instance, nausea, a common side effect of selegiline, could have caused this uptick in processing information related to disgust. However, there is no indication of such an effect in the taste reward task, nor is there any evidence that experiencing nausea would increase the processing of disgusted

faces. Alternatively, it could suggest an increase in the processing of negatively valenced stimuli as a whole. When combining this result with the other emotional processing tasks, namely ECAT and EREC, the potential increase in the processing of negatively valenced emotions is not replicated elsewhere.

EREC, in particular, shows an increase in the correct recall of positively valenced stimuli for the active group. Similarly, while FERT does not show an increase in the correct categorisation of happy faces in the selegiline group, there is an increase in falsely labelling faces as happy. Given that the number of happy false alarms is low, it is currently not possible to determine whether this is due to a positive bias, where negatively valenced faces are being categorised as happy, or whether other positively valenced faces are being categorised as happy. If it is the latter, then this would mean the false alarm is related to decreased processing of the arousal axis.

On the other hand, the results of EREC could also be interpreted as an increase in memory skills overall. While not reaching the threshold for statistical significance, a higher sample size in a replicated study could potentially reveal that the increase in correctly recalling stimuli is not influenced by valence but rather by an enhancement in the faculty of memory itself. Dopamine crucially modulates hippocampal synaptic plasticity, enhancing it through various receptors and pathways (Tsetsenis et al., 2023). For example, dopamine in the dorsal hippocampus, binding to D1/D5 receptors, promotes attention, episodic memory, spatial learning, and synaptic plasticity (Kempadoo et al., 2016).

Studies with bupropion have found that an acute increase in dopamine enhances positive bias in the same or similar tasks (Walsh et al., 2018). However, research with Pramipexole has found no difference in behavioural results acutely and subacutely. (Halahakoon et al., 2023; Cowen et al., 2021) Though the fMRI results showed that the neural processing of fear in particular was found to be decreased. (Martens et al., 2021)

Overall, there is preliminary evidence to support that selegiline does induce a potentially positive bias. While there are some limitations to this interpretation, as discussed in D, the findings of the two different tasks correlate with one another and with other similar studies involving dopaminergic medications. Regarding the increase in sensitivity to disgusted faces, since it is above the p=0.1 threshold by 0.003, the result is a reflection of the natural variance of data rather than an effect of selegiline. Still, it is crucial to see if this would be replicated in a sufficiently powered study.

C. Putting it All Together: Integrating Findings from Reward and Emotional Tasks

Both reward and emotional processing have various components that also appear to be impacted by selegiline differentially as well. As discussed in the introduction, selegiline was expected to induce positive bias in emotional processing by way of positive bias in reward processing. The introduction posited that selegiline would boost dopaminergic circuitry activity in the brain, enhancing specific facets of reward processing and consequently leading to a positive bias in emotional processing. This argument hinges on the assumption that the valence computed by the ventral striatum, influenced by phasic dopamine, aligns with the valence computed in the amygdala, which, in turn, receives inputs from dopaminergic VTA neurons. While there is tentative and inconclusive evidence suggesting a positive bias in emotional processing, the opposite trend is robustly supported for reward processing and particularly *reward sensitivity*. This is especially evident when considering the concurrent processing of reward stimuli, as opposed to a mere 'theoretical' or 'anticipated' reward.

There are a few other examples of a dissociation between the valence computation in the reward circuitry and emotional circuitry when other dopaminergic medications, such as bupropion, are used. In an acute study, bupropion was found to

induce positive bias in emotional processing but impaired reward bias. (Walsh et al., 2018)

Neuroanatomically speaking, there are a variety of explanations for the dissociation of valence computation in reward and emotional processing. As can be seen in Figure 1, there are and should be different algorithmic approaches to computing valence in the brain. (Tye, 2018) Some valences depend on learning, others do not, and some associations need to be compared more intensely than others. Some theories in the introduction postulated that reward processing and emotional processing use the same informational backbone, the computation of valence. (Breiter and Gasic, 2004) While this research is far from dismantling this assertion, the field of valence computation appears to be ripe for further study. Many of the putative hierarchically-organised processes are potentially computed in parallel. Understanding and distinguishing between different types of affective phenomena will require how each processes and utilises valence specifically.

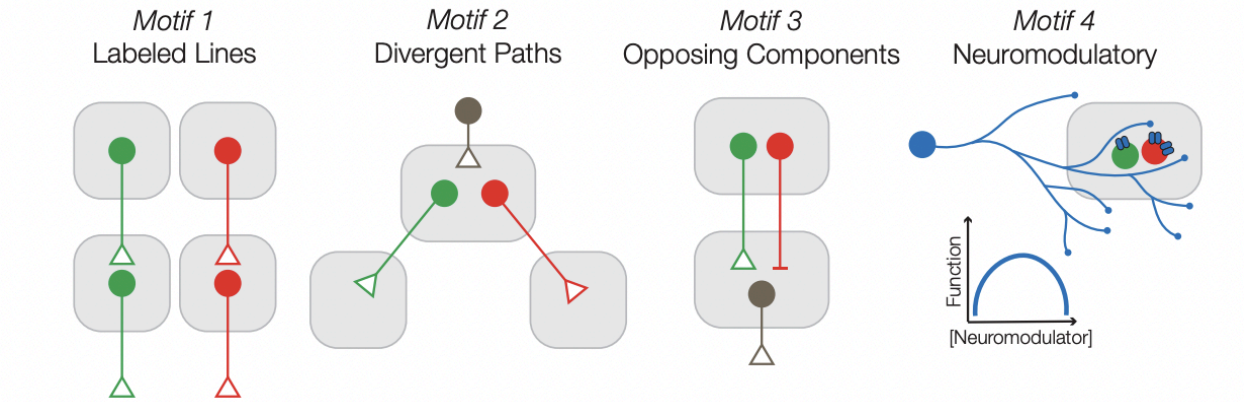

Figure 1: The four motifs elucidate distinct organisational principles in neural circuits. Motif 1: labelled as "*Labelled Lines*," portrays a circuit with parallel sensorimotor paths for positive and negative stimuli, directly relaying to downstream circuits governing approach and avoidance independently. This configuration ensures the algorithmic advantages of speed and robustness. Motif 2: "*Divergent Paths*," highlights a circuit receiving uniform sensory input but diverging to distinct downstream targets guided by synaptic weights, offering associative plasticity, flexibility, and reversibility. Motif 3: "*Opposing Components*," outlines a circuit with neurons of diverse functionality within a defined projection, facilitating coordination, regulation, and weighing of various inputs. Motif 4: "*Neuromodulatory Gain*," delineates a circuit where concentration-dependent

activation of metabotropic receptors extends plasticity timescales, enabling single-trial learning, state dependency, and context switching. Together, these motifs provide insights into the varied organisational strategies employed by neural circuits.

The 4th Motif in Figure 1 is the most relevant for dopamine as it communicates how metabotropic receptors could integrate learning and valence. The idea relayed postulates that neurotransmitters with metabotropic receptors require optimal levels to encode positive valence. Low levels of catecholamines result in low arousal and decreased executive function, while moderate catecholaminergic innervation leads to optimal arousal and higher cognitive function. However, an imbalance in dopamine levels, either excessive or insufficient, in the prefrontal cortex (PFC) can impair executive function (Tye, 2018; Arnsten, 1997, 2009; Hu, 2016), contributing to depression-like symptoms (Tye, 2018; Chang and Grace, 2014; Chaudhury et al., 2013; Lammel et al., 2014). Dopamine plays a dual role, regulating plasticity in the amygdala for fear conditioning and reward-related learning, while also influencing positive valence in the ventral striatum and negative valence in the PFC (Tye, 2018; Bissière et al., 2003; Tye et al., 2010a; Tsai et al., 2009; Witten et al., 2011; Gunaydin et al., 2014; Lammel et al., 2011, 2012). Furthermore, this answers why exogenous dopaminergic interventions result in disconcerted valence computation. Perhaps the algorithm followed in this motif explains why reward sensitivity and reward learning are so difficult to distinguish from one another. This motif is also crucial for switching between valences for specific stimuli. (Tye, 2018)

The question then remains how a dopaminergic medication induced positive bias in emotional processing if not through reward processing. Dopamine release into the striatum during emotional processing has been directly observed, providing evidence of dopaminergic modulation of human emotional processing at multiple levels (Badgaiyan et al., 2009; Badgaiyan, 2010). Potentially, the dopaminergic circuitry's influence on the amygdala could be the driving force behind this possible positive bias. Some studies show that the emotional disturbances in PD correlate with the amygdala's abnormal function. (Tessitore et al., 2002) Other literature focuses on linking emotional valence with dopamine through learning. (Laviolette et al., 2005)

Finally, these also point towards a new theoretical framework for how we define valence within the context of emotional processing. Much of positive/negative valence attribution to emotions relies on supposed pleasure or pain and potentially reward or punishment markers. (Prinz, 2009) As discussed in the introduction, most of the particular definitions of affective scientific phenomena utilise a specific philosophical framework that echoes the presumptions of its time. While the existence of two polar valences is supported by divergent neural circuitries, phenomenological embodied experiences, and divergent succeeding behaviour patterns, the question of how to explain these two polars and what they mean is less conclusive in the literature. Understanding how affective phenomena compute, utilise, and consequently conceptualise valence could be a crucial distinction enabling us to delineate between them.

D. A Few Caveats in the Interpretation

The discerned noise, as evidenced by elevated standard deviations and residuals, collectively advocates for more comprehensive exploration and suggests that the study is underpowered. This highlights the need for a larger sample size to render definitive statements about the observed results. Additionally, the sample size was lower than 20 for some of the tasks. Thus, it is essential to note the ways in which the small sample size could have contributed to the results summarised in A. Although the small sample size might potentially elevate the p-value of the alternative hypothesis by introducing more noise, it could also have the opposite effect. The presence of noise in the data would artificially increase the standard deviations, thereby making it more challenging to discern differences within the data.

Similarly, an exploratory approach was observed when conducting the statistical analysis. For instance, even though no statistical significance emerged from the ANOVA results, post-hoc tests were still carried out. This could have culminated in the problem of multiple comparisons, where the exploratory analysis might have yielded false positives. The p-value, which is set at 0.1, is already quite high compared to the

orthodox 0.05, and should have been reduced even further. Thus the significance of the results should be further scrutinised by the reader. On the other hand, the conservative Greenhouse-Geisser correction was used when there was a violation of sphericity; however, given the small sample size, which could have further underpowered the study.

Another caveat in interpreting the results echoes concerns present in other studies exclusively reliant on behavioural tasks. Notably, there is a notable absence of tasks specifically designed to assess the cognitive effects of selegiline. This gap makes it challenging to attribute changes in emotional or reward processing solely to the use of selegiline. The dearth of task variety underscores the complexity of understanding the broader cognitive implications of this medication. Issues with the tasks further compound the complexity of the study. Participants may find certain tasks, especially those related to rewards, trivial. Moreover, using money as a reward introduces a contentious element, as it is more susceptible to individual differences across groups, including current and past socioeconomic status. This introduces a potential source of bias, adding complexity to the interpretation of results. A larger sample size could potentially mitigate these confounding effects, providing a more robust foundation for drawing conclusions. Furthermore, the compensation of EEfRT relied heavily on chance, causing disillusionment with the task from the onset. There is strong reason to believe, due to participant feedback that this deterred from fully engaging with the task.

Additionally, the interpretation of side effects, particularly nausea, is hampered since it was not systematically collected. This insufficiency poses challenges in comprehending the potential impact of side effects on the overall study outcomes, contributing to a significant gap in our understanding.

Furthermore, there are some important limitations that undermine some of the positive findings. The placebo group exhibited significantly elevated trait anxiety scores on the STAI-T questionnaire, which may have contributed to the observed positive emotional bias rather than being an effect of selegiline. The lack of statistical analysis that accounts for the STAI-T results as a confounding factor precludes us from making definitive statements about the positive emotional bias. Similarly, the taste reward task used the difference between the two task sessions for analysis. Thus, it is possible that the

placebo group initially had exceptionally high anticipation, resulting in regression to the mean, while the selegiline group remained the same. This potential bias should have been addressed by measuring baseline anticipation levels before the intervention and incorporating these measurements into the analysis. Statistical methods, such as including baseline anticipation as a covariate in regression models or conducting subgroup analyses, would have helped determine whether changes observed are attributable to selegiline's impact on baseline or second anticipation score.

Moreover, there was no systematic collection of allocation guesses, partly due to the ambivalence of most participants. Thus, we are not capable of ensuring a double-blind study through data.

Finally, when attempting to assess the potential of selegiline in depressed individuals, other limitations come to the forefront. The study population comprises a non-clinical group with likely optimal baseline dopamine levels and functional connectivity in dopaminergic circuitries. This characteristic introduces challenges in extrapolating the findings to a clinical context, limiting the generalisability of the results.

E. Determining Oral Selegiline's Efficacy and Future Directions

As outlined in the introduction oral selegiline has not been considered effective in terms of ameliorating depressive symptoms. (Patkar et al., 2014) Nevertheless, the current literature falls short of providing a complete picture. While some research employs potential serotonergic effects as a benchmark in assessing efficacy, others do not distinguish between subtypes of depression. This research utilised the so-called *cognitive neuropsychological model of antidepressant action* to provide an alternative framework to evaluate selegiline's therapeutic capacity in depression. The aforementioned framework posits that one-way antidepressants have a therapeutic impact on depressed patients is by promoting a positive emotional bias. (Godlewska and Harmer, 2021) In line with this model, single-dose oral selegiline can potentially be of use in depression since there

is evidence that it induces positive emotional bias. However, a bigger sample size is needed in order to make a definitive statement in regard to positive emotional bias.

To begin with, selegiline also appears to positively influence relevant aspects of reward processing: *anticipation*. As argued in the introduction, impairments in anticipation or wanting are crucial in developing and sustaining anhedonia. Conversely, it could be impeding reinforcement learning or reward bias, also potentially important components of reward processing in depression. In order to make more definitive statements on how selegiline and especially other dopaminergic medications acutely impacts reward processing, future studies should involve behavioural tasks that fully distinguish between reward bias and reinforcement learning. Moreover, generally speaking, reward tasks used in depression research should perhaps be more geared to assess the symptoms observed in depression. These tasks should be further validated for anhedonia and other more specific reward-related depressive symptoms. On another note, these criticisms are also relevant to nearly all acute assessments of reward processing used to ascertain antidepressant properties.

Given selegiline's beneficial impacts on the anticipation aspect of reward processing, testing its efficacy in particularly depressed patients whose symptoms most likely point towards an impairment in that aspect. Similarly, patients that have found BAT beneficial could also benefit from medication that ameliorates *wanting*. When comparing selegiline to other antidepressants and also dopaminergic medications, it appears to be a promising candidate. Overarchingly though, current data shows that selegiline's acute impact appears mild in comparison.

Furthermore, subacute and longitudinal studies that use similar behavioural tasks could shed more light into the progression of selegiline's behavioural effects and whether they do in fact translate into ameliorating depressive symptoms. Also, studies that distinguish between selegiline's cognitive and affective effects are required to scrutinise its antidepressant potential. Similarly, fMRI studies would showcase the neural correlates of selegiline's mechanism of action. Still, more invasive techniques might be needed using animals with a similar MAO-A and MAO-B distribution.

Considering the involvement of dopamine in the computation of aversive stimuli and the potential for better functioning in the functional connectivity of aversive circuitry, there arises a concern that these medications could contribute to the worsening of anhedonia. This highlights the need for careful consideration when prescribing such medications, especially in individuals with already well-functioning aversive circuitry.

Moreover, there is a gap in the literature regarding fully understanding the effects of selegiline on the human central nervous system. PET scans on humans and microdialysis on animals with a similar MAO-A and MAO-B distribution could produce a more complete picture of its effects. Currently, the literature is confined to selegiline's beneficial neurological effects. However, psychiatric formulations and manipulations require a more in-depth understanding of how the implementation level impacts the computational level. Likewise, further research specifying MAO-B distribution, especially in the striatum, and selegiline's impact on other non-dopaminergic systems would be useful.

On a different note, the conflicting results of this research do evoke curiosity about the dopaminergic circuitry. Definitive answers into why its global increase might be detrimental to reinforcement learning could be useful for understanding other psychiatric disorders, such as schizophrenia, but would also provide the infrastructure for manipulating this system for depression. Furthermore, understanding the dopaminergic system would answer one of the most fundamental questions in neuroscience: how is value ascribed in the brain. The only way to fully understand it would require research incorporating all of Marr's levels and how they interact.

Mood is an intangible and broad affective phenomenon that is bigger than the sum of its parts. Perhaps these investigations demonstrate the need for a new conceptual framework for defining valence within the context of affective phenomena, especially in emotional processing. Much of positive/negative valence attribution to emotions relies on supposed pleasurable or painful attributes and/or potentially reward or punishment markers. (Prinz, X) As discussed in the introduction, most of the particular definitions of affective scientific phenomena utilise a specific philosophical framework that echoes

the presumptions of its time. While the existence of two polar valences is supported by divergent neural circuitries, phenomenological embodied experiences, and divergent succeeding behaviour patterns, the question of how to define these two polars is less conclusive in the literature. Future endeavours in affective science should be mindful of how phenomena are conceptualised in their research.

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