Social and economic decision-making in Urbach-Wiethe Disease

Dissertation submitted in the fulfilment of the requirement for the award of the degree

Masters of Science (Medicine) in Neuroscience of Psychiatry by dissertation

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Compulsory Declaration

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced accordingly.

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Signature: Signed by candidate Date: 29/01/2020

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Acknowledgements

This study was supported by funding awarded to Prof van Honk and Prof Stein, and from funds awarded by the University of Cape Town Department of Psychiatry.

This project is dedicated to the amazing people of Namaqualand, who made us feel so at home for the past few years. To every participant who helped us to make valuable contributions to neuroscience and to their inextinguishable zeal for life, despite personal hardships. You are an inspiration.

To my family: Ma and Pa, and siblings, for their unwavering support. It has been a rollercoaster ride, thank you for being by my side. For mustard-seed faith, knowing I can do all things through Christ who strengthens me. For the people who have played an important role in my slow journey in Neuroscience: Prof Steinmann, who ignited the love for research in me; my supervisors, Prof van Honk and Prof Stein, for their valuable inputs, opportunity to be part of the project and patience. Lisa and Michael, who were never too busy to give advice on my statistics, even when I had no idea what I was doing. David Terburg, for the assistance with imaging questions and results.

To Louw, for being my home.

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BLA	Basolateral amygdala
CMA	Centro-medial amygdala
OFC	Orbitofrontal complex
ACC	Anterior cingulate cortex
NAc	Nucleus accumbens
dlPFC	Dorso-lateral prefrontal cortex
PFC	Pre-frontal cortex
vmPFC	Ventro-medial prefrontal cortex
UWD	Urbach-Wiethe Disease
ECM1	Extra-cellular matrix protein 1
fMRI	Functional magnetic resonance imaging
CUBIC	Cape Universities Brain Imaging Centre
WAIS III	Wechsler Adult Intelligence Scale III
WASI	Wechsler Abbreviated Scale of Intelligence
GLS	Generalised Least Squares statistical model
sgACC	Subgenual anterior cingulate cortex

Abstract

Background: Rodent and primate research have identified the basolateral amygdala as indispensable for social decision-making. This finding has not yet been translated to humans, and has even been partially contradicted by previous findings in patients with amygdala lesions that show generous economic investments in strangers. This thesis therefore aimed to determine whether selective basolateral amygdala damage in humans, caused by Urbach-Wiethe Disease, impairs instrumental non-social economic decision-making.

Methods: Using an adapted reinforcement-learning task, the performance of basolateral amygdala damaged individuals (n=6) was compared with that of healthy controls (n=20) on social and economic decision-making during a probabilistic reinforcement task. The task required participants to make decisions for themselves and others based on learned probability of monetary reward or loss. A random effects Generalised Least Squares regression was conducted using Stata 15.1. to assess discrimination between Gain and Loss domains. A social-decision making task was also administered.

Results: When making choices for themselves, Urbach-Wiethe Disease participants showed no difference in correct choices made between Gain and Loss domains. The Urbach-Wiethe disease participant's lack of discrimination between gains and losses for themselves was significantly different ($p<0.01$) from that of controls, who made significantly more correct choices for themselves in the gain domain compared to the Loss domain. Social decision-making performance did not, however, differ significantly between Urbach-Wiethe Disease participants and controls.

Conclusions: These findings regarding non-social decision-making support the important role of the basolateral amygdala as a salience detector, with lesions to this region resulting in reduced bias to the valence of potential economic outcomes, regardless of whether these pertain to costs or benefits. These findings are also consistent with prior work indicating that lesions to the basolateral

amygdala can possibly produce loss-aversion due to a hypervigilance for fear and the lack of inhibition of the centromedial amygdala by the basolateral amygdala.

1.Introduction

1.1 Background

The neural processes underlying decision-making are highly complex and crucial to the survival of species. All organisms display reward-seeking behaviours, from the associative conditioned migration of amoeba towards a chemoattractant (Ildefonso, et al., 2019) to phototropic solar tracking seen in sunflowers (Kutschera & Briggs, 2015), however it is the complex ability to analyse choices by their future outcomes and context-specific subjective values that affords higher vertebrates the tools to make decisions that go beyond purely reward-seeking behaviours. Humans, like all animals, are fundamentally decision makers as everyday life presents to us endless choices: from deciding what time to wake, what to wear, where to go, how to thrive, who to trust. By understanding the principles of decision-making and the intricate neural pathways involved, we can uncover the mechanisms that underlie core cognitive functions (Shadlen & Kiani, 2013).

Over the past decade, decision-making research has delved deeper into topics of learning, memory, risk, reward and motivation: all fundamental building blocks of cognition. The amygdala and its subnuclei are considered essential in these cognitive processes as this structure shares rich interconnections with other brain regions, including the prefrontal cortex (PFC). Through rodent and primate research, we have made great strides in beginning to understand the complex neural mechanisms involved in decision-making. Nevertheless, the translation of these findings to decision-making in humans remains challenging. The amygdala, which is still mostly researched as a unified structure despite its heterogenous components, and it is rare to find humans with specific lesions to amygdala subnuclei.

The majority of studies on human decision-making use imaging data to determine the involvement of brain regions during each component of the decision-making process. These neuroimaging studies, although useful, are often correlative and lack the ability to draw definitive conclusions in the absence of causal evidence (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). Natural lesion

studies can fill this gap by providing strong causal inferences about the role of specific brain regions and their interactions. Human lesion research affords important insights into the mechanisms involved in thoughts, behaviour and cognition, as these processes are dependent on the functionality of various converging neural structures and pathways.

Specific lesions in humans are mostly caused by trauma, surgical removal or stroke, and are often unilateral with vague borders. Urbach-Wiethe Disease (UWD) is a rare autosomal disorder that can present with specific neural lesions in humans. These lesions are highly selective and often bilateral, which provides a unique opportunity to conduct research on the specific role of amygdala subregions in affected individuals. A cohort of UWD individuals in Namaqualand, South Africa, has been identified with selective bilateral basolateral amygdala (BLA) lesions.

In humans, very little is known about the unique role of the BLA in social and economic decision-making. In rodent research, the BLA has been shown to have rich interconnections to areas such as the dorsolateral prefrontal cortex (DLPC), nucleus accumbens (NAc), centro-medial amygdala (CMA) and orbitofrontal cortex (OFC). Translating results from mammalian social and economic decision-making to humans is difficult as humans possess future-thinking that differs greatly from primates and rodents.

In this chapter I will discuss current knowledge of social and economic decision-making in humans and the neural structures involved. I will highlight the gaps in research on this topic conducted in humans and explore new possibilities afforded by lesion studies. I will also discuss Urbach-Wiethe disease and how a small cohort of South African individuals affected with specific lesions caused by this rare disorder have already contributed to understanding of emotion, learning, memory, and social- and affective behaviours. Finally, current and future opportunities for research on human decision-making in this small cohort will be discussed.

1.2 Urbach-Wiethe Disease

1.2.1 History and aetiology

Urbach-Wiethe Disease (UWD) was first termed *Lipoidis cutis et mucosae* by two Austrian clinicians, dermatologist Eric Urbach and otorhinolaryngologist Camillo Wiethe in 1929. It is also known as *lipoid proteinosis* or *hyalinosis cutis et mucosae* (Urbach & Wiethe, 1929).The exact incidence and prevalence is not known although males and females seem to be equally affected and incidence is higher amongst individuals with consanguineous parents (Holme, Lenane, & Krafchik, 2005). UWD is one of the rarest recessively inherited autosomal disorders, caused by various homozygous loss-of-function mutations in the extracellular matrix protein 1 (ECM1) gene which is located on chromosome 1q21 (Hamada, et al., 2002). There are currently fewer than 100 cases known to exist now worldwide (van Honk, Terburg, Thornton, Stein, & Morgan, 2016) and fewer than 250 (Hamada, et al., 2002) to 300 (Botha & Beighton, 1983) cases have been documented in the past. Severity of clinical manifestations appear to be more pronounced in individuals with exon 6 mutations than those with exon 7 mutations, although findings on exact systemic correlation between clinical features and genetic mutations are lacking (Hamada, et al., 2003).

Nearly half of the worldwide identified UWD population lives in South Africa. Stine and Smith investigated the reason behind this fascinating statistic in 1990. They attributed the high incidence of this otherwise exceptionally rare disease to a founder effect. It is believed that Jacob Cloete, one of the early German settlers to arrive in South Africa, introduced the ECM1 mutation to local Dutch settlers in the Cape Colony (Stine & Smith, 1990). The mutation was later spread to the small community of isolated indigenous inhabitants from Namaqualand in the arid, semi-desert province of the Northern Cape about 300 years ago by a descendent of Jacob Cloete. Within this secluded and genetically homogeneous population, the mutation was amplified, so leading to Namaqualand currently being home to the largest population of UWD in the world (Thornton, et al., 2008; Van

Hougenhouck-Tulleken, et al., 2004). Another group of South African UWD participants from Gauteng province, all Caucasian, have also been identified and investigated (Thornton, et al., 2008).

Within the South African population of UWD patients, the specific variant of the ECM1 mutation has been identified as Q276X, located in exon 7 (Hamada, et al., 2002). 9 other mutations have however associated with UWD worldwide, each with varying degrees of dermatological pathology. Even though the South African patients share a common mutation in the EMC1 gene, a considerable amount of clinical variability persists in terms of severity of symptoms and clinical manifestations (Van Hougenhouck-Tulleken, et al., 2004).

1.2.2 Clinical manifestations, diagnosis and treatment

Individuals with UWD mostly present with variable signs of stridor from early childhood, or a typical hoarsened cry at birth (Hofer, 1973). Other otolaryngologic manifestations that have been seen in patients include oedema and thickening of the lips and tongue, dysphonia and dysphagia due to mucocutaneous involvement of the larynx, thickening of the lingual frenulum which leads to ankyloglossia, and varying degrees of dental anomalies (Nanda, Alsaleh, Al-Sabah, Ali, & Anim, 2001). In early childhood, some patients develop inflammatory wax-like skin lesions resembling pox or acne, whilst scarring on the face, trunk, dorsum of hands, feet and elbows may be present due to extensive amorphous hyaline-like depositions, especially areas affected by sun exposure or minor trauma (Urbach & Wiethe, 1929). Papular beading around the eyelid margins is also a common feature (Kachewar, Singh, Sesane, & Bhadane, 2011). Hyaline deposits can occur in UWD patients on the cornea and conjunctivae, mimicking age-related degenerative cataracts (Oyama & Merregaert, 2017). Occasional compromised dermal regeneration is expected, as ECM1 is a glycoprotein implicated with dermal homeostasis, often referred to as an essential scaffolding protein (Chan, Liu, Hamada, Sethuraman, & McGrath, 2007), see Figure 1 below.

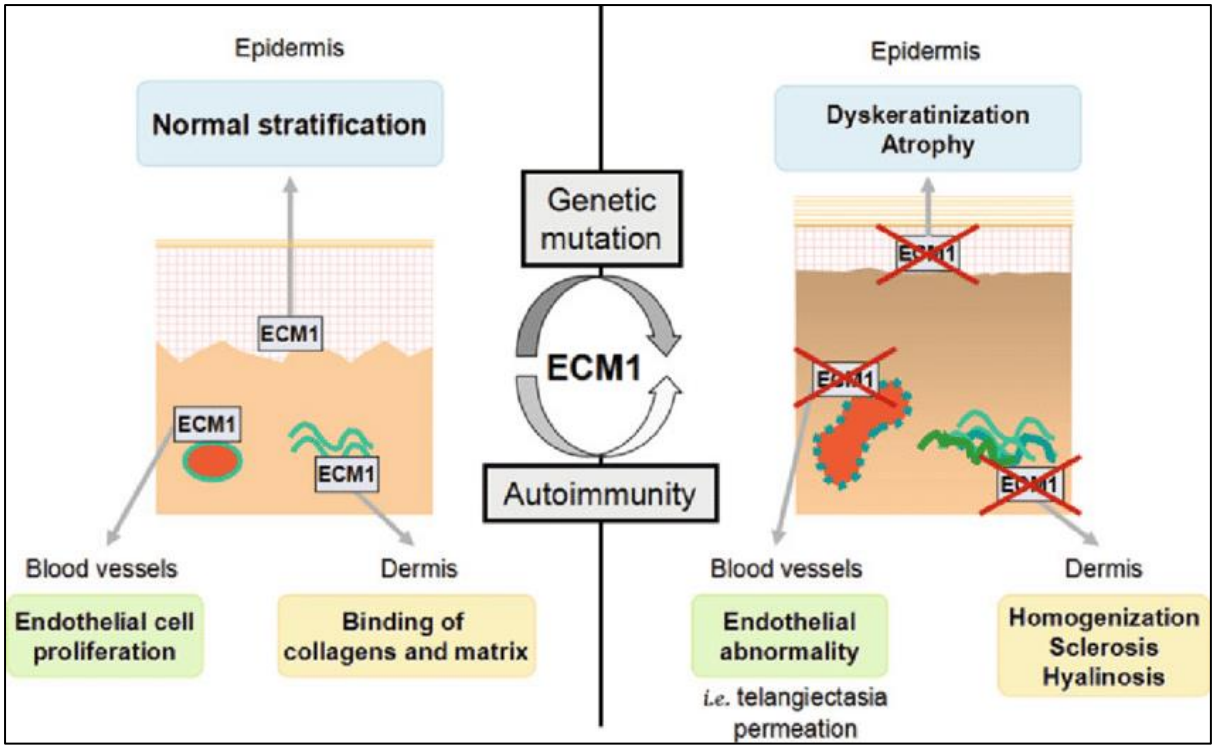

Figure 1: ECM1 loss-of-function mutations in Urbach-Wiethe Disease (Oyama & Merregaert, 2017)

Extracutaneous manifestations have been reported in patients with UWD, including visceral pathologies, epileptic seizures (Appenzeller, Chaloult, & Velho, 2006), paranoia and aggression (Matthies, Rusch, & Weber, 2012), abnormal emotion recognition (Adolphs R. , Tranel, Damasio, & Damasio, 1994; Siebert, Markowitsch, & Bartel, 2013), depression (Wiest, Lehner-Baumgartner, & Baumgartner, 2006), and migraines and headaches (Claeys, Claes, & Van Goethem, 2007). Where neuropsychiatric comorbidities are detected, neuroimaging often reveals calcifications within the temporal lobes, specifically the amygdala, however these can be present without any mental symptoms. Although amygdala involvement is present in almost half of the known UWD population, a number of reports show more extensive intracranial calcifications in the hippocampal region and striatum (Goncalves, de Melo, de L Matos, Barra, & Figueroa, 2010). Individual variation in calcification is still not fully understood, however differences in the specific variant of loss-of-function mutation may play a role (Hamada, et al., 2002). The lesions found in UWD patients

progress with age and are mostly focal and bilateral with no known impact on life expectancy (Adolphs R. , Tranel, Damasio, & Damasio, 1994) (Koen, et al., 2016; Hurlemann, et al., 2009).

Diagnosis of UWD is complex due to the diverse nature of mucocutaneous and extracutaneous manifestations in affected individuals. Differential diagnoses include congenital hypothyroidism (Parida, Misra, & Agarwal, 2015), chronic laryngitis, erythropoietic protoporphyria, papular mucinosis, laryngeal amyloidosis, xanthomatosis, laryngeal neoplasm and vocal cord polyp (Xu, Wang, Zhang, Han, & Zhang, 2010; Holme, Lenane, & Krafchik, 2005). UWD is differentiated histologically by positive results on periodic acid-Schiff staining and negative results on Congo red staining of deposits in biopsies from the submucosa and dermis (Xu, Wang, Zhang, Han, & Zhang, 2010). Possible radiological diagnosis is obtained from evidence of bilateral calcifications. Genetic testing can be conducted to investigate the presence of mutations in ECM1 (Hamada, et al., 2002).

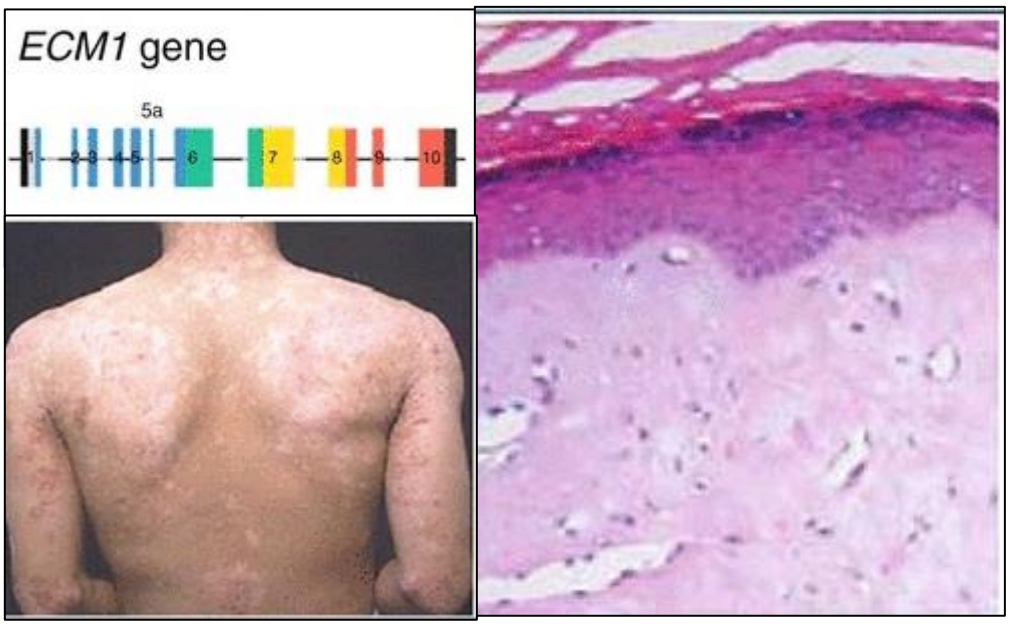

Figure 2: Histological (PAS-positive) and dermatological presentation of Urbach-Wiethe disease due to ECM1 mutations (Oyama & Merregaert, 2017).

Treatment is palliative and aimed at improving the quality of life. Most therapeutic interventions addressed either aesthetic concerns or laryngeal involvement to improve speech, breathing and swallowing. Patients are often prescribed acitretin, oral steroids, subcutaneous heparin injection,

oral dimethyl sulphate or D-penicillamine (Kachewar, Singh, Sesane, & Bhadane, 2011; Conti & Arnone, 2015; Gündüz, Şahiner, Atasoy, & Şenyücel, 2012). However there have been mixed results, and few definitive controlled studies with sufficient power. Carbon dioxide laser surgery may decrease the appearance of beading around the eyes, whilst dermabrasion therapy may improve the appearance of dermal irregularities, specifically scarring on the face (National Institute of Neurological Disorders and Stroke, 2016). Anti-convulsant medication is used in patients with secondary epileptic episodes and should be individualised to the specific needs of the patient. With the presentation of significant airway obstruction due to laryngeal or vocal cord thickening, a tracheostomy may be necessary (Vahidnezhad, Youssefian, & Uitto, 2016). Microlaryngoscopic excision of laryngeal deposits may however prevent the need for a tracheostomy; this highlights the importance of early diagnosis and intervention.

1.2.3 The amygdala in Urbach-Wiethe Disease

In a single case study of UWD, a female patient referred to as SM046, was first reported in 1990 with selective bilateral amygdala damage and has subsequently been described in the literature as the "woman without fear" (Tranel & Hyman, 1990). SM046 is an otherwise healthy individual who functions within the normal ranges of intelligence, language and skin conductance responses (Tranel & Hyman, 1990). She has however shown significant deficits in emotion recognition from facial expressions, trustworthiness ratings of strangers, and the expression and experience of fear; has impaired declarative memory for emotionally salient events; and also doesn't adhere to socially accepted standards of personal space (Adolphs & Tranel, 2003) (Adolphs, Tranel, & Damasio, 1998; Adolphs R. , Tranel, Damasio, & Damasio, 1994). Adolphs et al later proposed that SM046's inability to recognise fear from facial expressions can be attributed to her inability to instinctively fixate on the eye region of faces (Adolphs, et al., 2005).

Unlike externally triggered fear, a different mechanism for internally triggered fear is theorised, since, despite her bilateral amygdala lesions, SM046 still experienced fear and panic during CO_2

inhalation (Feinstein, et al., 2013). Research conducted on SM046 has contributed greatly to current understanding of the amygdala's role in social and affective behaviour, however these findings reflect the deficits from total amygdala calcification. With most of the information about the human amygdala stemming from total loss of function, questions remain unanswered about the function of the subregions of the amygdala: the BLA and CMA.

1.2.4 A very unique cohort

The Namaqualand cohort of individuals affected by UWD described earlier in this chapter, has been extensively involved in research since as early as 1970 (Hofer, 1973; Heyl, 1970). The proportionately large group of 27 homogenous patients in small rural communities surrounding Springbok in the Northern Cape Province performed poorly in facial recognition tasks (not specific to fear), achieved lower scores in various IQ measures compared to controls and had a higher incidence of anxiety disorders (Thornton, et al., 2008). Unfortunately, the extent or presence of neural lesions in the entire group of studied individuals is not known as imaging data was not collected.

Notably, the rural communities of Namaqualand are stricken with poverty, especially after the major exodus of copper and diamond mining companies that once brought vast employment opportunities to these regions. The current inhabitants are mostly unemployed, dependent on governmental subsidies, and have limited access to educational, healthcare and developmental facilities. Substance abuse is common, especially in men from this community, leading often to secondary psychopathologies. These factors can often result in misleading results from scientific research and thus a smaller cohort was selected for further research. This cohort only consisted of five females, as UWD individuals with secondary psychopathologies, epileptic insults or substance abuse were excluded. Another reason for the selection of only females was to make more accurate associations with findings from European cases and SM046, whom are all female (Van Honk J. , 2009).

This small subgroup of female UWD individuals in Namaqualand has been studied to gain insights on UWD progression as well as the roles of specific subregions of the amygdaloid complex. The group of

otherwise healthy females (aged 32 – 58 years) have no secondary psychopathologies or history of epileptic insults. They have IQ scores within the low-normal range for non-Western participants (Morgan, Terburg, Thornton, Stein, & van Honk, 2012), after the Wechsler Abbreviated Scale of Intelligence was properly translated into their mother tongue (Wechsler, 2011). These IQ results were not, however, significantly different from those of matched controls. This differs from initial findings from the larger study population in Namaqualand by Thornton and colleagues (Thornton, et al., 2008), who showed that the UWD population had IQ deficits in areas of memory and executive function, unlike their matched controls. Disparities in these results could be due to the exclusion of individuals with comorbid psychopathologies (Koen, et al., 2016) as well as the implementation of an abbreviated assessment tool in the smaller cohort (Wechsler, 2011).

Determining the extent of neural damage

Calcification of certain brain structures is often seen in UWD and individual investigation is necessary as these lesions lack uniformity: a possible result of varying exon mutations within the disease. Structural as well as functional magnetic resonance imaging (MRI) was used to determine the extent of amygdala calcifications in the Namaqualand cohort of UWD affected women. T2-weigted whole-brain scans were obtained for lesion analysis at the Cape Universities Brain Imaging Centre (CUBIC) using a 3-Tesla Siemens Magnetom Skyra MRI scanner. Given extensive inter-subject variability, magnetic resonance images alone are unable to provide precise locations and borders of lesions both between structures and within sub-structures (Amunts, et al., 2005). To establish individual subregional damage within the amygdala, T2-weighted scans were first used to create 3D lesion volume images and normalized to standard stereotaxic space in MRIcron (Rorden & Brett, 2000). These standardized images for volume-of-interest were then superimposed onto probabilistic cytoarchitectonic maps of the amygdala and hippocampal regions, based on post-mortem human brains (Eickhoff, et al., 2005). To further establish spared functionality within the amygdala, functional MRI scans were conducted whilst participants took part in an emotion-matching task,

which activates the whole amygdala simultaneously (Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002).

Using the MRI lesion-overlap probability technique above, neural damage was determined to be localized in the basolateral amygdala (BLA) almost exclusively and bilaterally (Terburg, et al., 2012) (See Figure 5). The results were also confirmed with quantitative analysis, showing that other subregions of the amygdala (centromedial and superficial) were unaffected and were significantly activated during the fMRI emotion-matching task (Terburg, et al., 2012). The damage seen in this group of women is considerably less extensive than the lesions in other well-documented cases of UWD in females, such as SM046 and other European subjects who exhibit either partial or complete CMA calcifications (Koen, et al., 2016).

These specific bilateral lesions of the human BLA are unique and are likely due to the exon 6 mutation found in Namaqualand patients, which could preferentially target the cortical neural tissue that constitutes the BLA, without affecting striatal tissue of the CMA (Koen, et al., 2016). Having a study population with such specific bilateral calcification allows for ideal opportunities to investigate the role of the human BLA, something that has, until now, been nearly impossible. To understand the contributions made to current knowledge about the human BLA, let us first take a closer look at this subregion of the amygdala.

1.3 Basolateral Amygdala

The human amygdala is located medially within the temporal lobes and forms an important part of the limbic system. This almond-shaped structure comprises heterogenous nuclei (see Figure 3) with unique cytoarchitectonic, connective and histochemical properties has functionally distinct characteristics (Sah, Faber, Lopez de Armentia, & Power, 2003). The main constituents of the human amygdaloid complex are the central-medial and basolateral amygdala, with mainly striatal and cortical internal structures respectively (Balleine & Killcross, 2006). The BLA is widely considered to be the consolidating evaluative centre of the brain, distinguishing between novel/significant and

unimportant input. It analyses the valence of sensory stimuli from prefrontal and thalamic sources, whereafter efferent fibres project to the CMA and prefrontal cortex (PFC), more specifically, the orbitofrontal cortex (OFC) (Davis & Whalen, 2001). On the other hand, the CMA is mostly considered the "dispatch" site in the amygdala, with output-projections to the brainstem and hypothalamus (LeDoux, 2007).

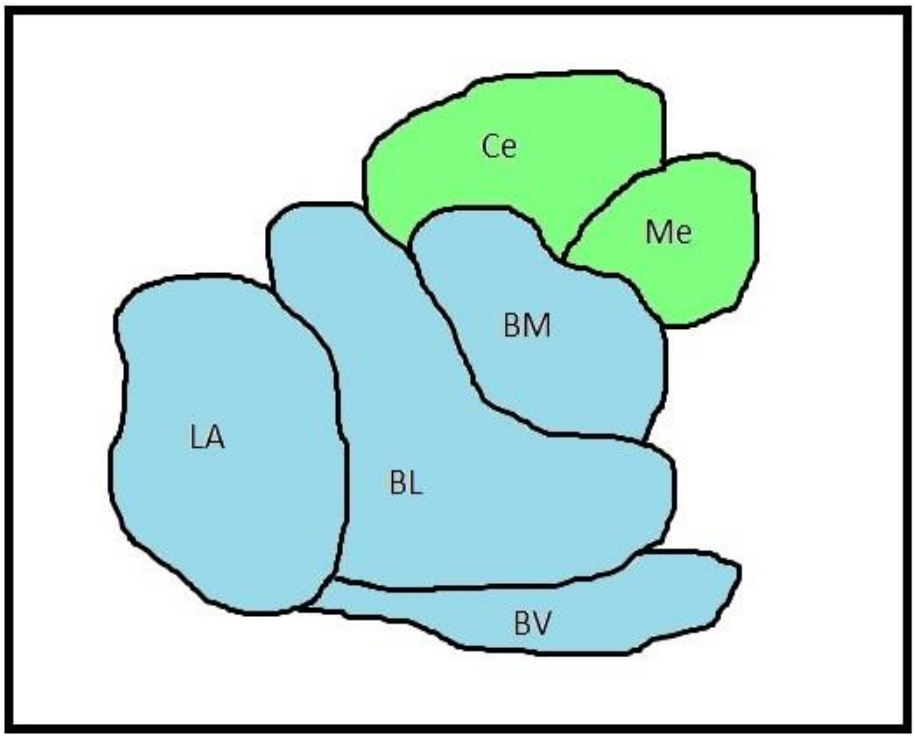

Figure 3: The amygdala is a heterogenous structure. Various functionally unique nuclei constitute the Basolateral Amygdala (blue) and the Centromedial Amygdala (green). LA: Lateral Nucleus. BL: Basolateral Nucleus. BV: Basoventral Nucleus. BM: Basomedial Nucleus. Ce: Central Nucleus. Me: Medial Nucleus.

Models of the amygdala's functionality are widely considered in the light of serial or parallel processing of information. The serial model was developed from research on aversive learning and suggests that the BLA forms associations from salient information that will eventually mediate defensive responses, by projecting these inputs to hypothalamic and midbrain regions via the CMA (Balleine & Killcross, 2006). The parallel processing model, which is widely accepted for appetitive conditioning, suggests that both the BLA and CMA function in parallel to integrate different conditional stimuli to produce motivated behaviour (Balleine & Killcross, 2006). Today, it is mostly

accepted that the BLA and CMA function independently and in parallel in both motivated and aversive processes.

Despite the different and often conflicting roles of the amygdala subnuclei, research on humans is still conducted on the structure as a single homogenous unit (Gupta, Koscik, Bechara, & Tranel, 2011). Nevertheless, the results from BLA lesioned animal models have given the scientific community a vast array of information about the role of this important relevance-detecting structure. The gradual effort to translate rodent and other mammalian studies of the BLA to humans has yielded a number of successes. For example, as was found in rodents (Hernandez-Lallement, van Wingerden, Schäble, & Kalenscher, 2016), in the Namaqualand cohort it was demonstrated that the human BLA is also crucial for social experiential learning (Rosenberger, et al., 2019), that the human BLA is responsible for instrumental, calculated behaviours (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013; Tye KM, 2011), and that the human BLA downregulates unwarranted fear (Terburg, et al., 2012). The results are often inconsistent with earlier studies on humans, as these were mostly conducted on individuals whose lesions are not specific to the BLA. Findings from rodent amygdala models of defensive behaviour, specifically the role of the BLA, have already been successfully translated to BLA damaged humans, indicating that the possibility exists that more rodent BLA functions are mirrored in humans (Terburg, et al., 2018).

1.3.1 Contributions from Namaqualand

Upon confirmation that the UWD cohort of Namaqualand patients had specific selective bilateral lesions to the BLA, continuous follow-up studies aim to form a deeper understanding of the human BLA's role in behaviour and cognitive processes and to translate findings of the BLA from non-human primate and rodent studies. Based on rodent studies, one would expect BLA damaged humans to show altered behavioural responses to innate fear (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). By evaluating the sensory role of the BLA in humans, a range of contributions have been made by studying the Namaqualand cohort of UWD women. I will focus on the contributions of the

BLA on working memory, fear responses, processing conflicting information, economic behaviour and learning.

Working memory

With vast thalamic and cortical projections, the BLA is considered to be the main sensory processing hub within the amygdala, competing for resources with the executive systems of the PFC (Davis & Whalen, 2001) via its connections to the OFC. The dorsolateral PFC (DLPFC) controls working memory and requires decreased amygdala activation to ensure sufficient performance during taxing working memory activity (Yun, Krystal, & Mathalon, 2010). The performance of working memory depends on the ability of the PFC to supress bottom-up regulation from the amygdala, especially during salient or emotionally arousing situations. As the BLA constantly regulates and interacts with the OFC, it surveys sensory inputs for salient information which will ultimately be conveyed to the DLPFC. Morgan and colleagues hypothesised that the absence of a functional BLA in humans would result in improved working memory as resources could be assigned to the executive systems of the PFC (Morgan, Terburg, Thornton, Stein, & van Honk, 2012).

To test this hypothesis, the Wechsler Adult Intelligence Scale III (WAIS III) digit span forward task was administered to three UWD participants from the Namaqualand cohort and ten matched controls. Working memory performance was significantly better in UWD participants than in controls (Morgan, Terburg, Thornton, Stein, & van Honk, 2012). This result, wherein neurological pathology results in enhanced performance, is considered a paradoxical functional facilitation (Kapur, 1996) and appears due to the unhindered activation of the DLPFC in the absence of a resource-diverting BLA salience detection system (Morgan, Terburg, Thornton, Stein, & van Honk, 2012).

These findings do however require confirmation by investigating working memory in these patients during taxing and changing situations. This can be done by administering validated working memory designs (Yun, Krystal, & Mathalon, 2010; Anticevic, Barch, & Repovs, 2010) during functional neuroimaging of the BLA and CMA as regions of interest in UWD and healthy controls (van Honk,

Terburg, Thornton, Stein, & Morgan, 2016). Future imaging studies can aim at determining the activity of the human salience network during non-threatening or resting conditions in order to support these findings.

Fear responses

The human BLA's role in threat detection is that of direct evaluation and identification of the potential danger, together with the indirect regulation by the OFC, to determine whether salient stimuli is indeed threatening (Mobbs, et al., 2007). As was found in rodent studies (Macedo, Cuadra, Molina, & Brandão, 2005; Martinez, de Oliveira, & Brandão, 2007; Graeff & Del-Ben, 2008), the human BLA also regulates the response to fear to prevent unwarranted hyperreactions to mild, distant threats (Mobbs, et al., 2007). This inhibitory regulation of the fear response by the BLA and OFC only occurs in the presence of a distant, avoidable threat. However, when the threat becomes impending and unavoidable or inescapable, the inhibition from the BLA/OFC is deactivated and the fear response takes over by means of activation of the CMA and PAG (Mobbs, et al., 2007). The BLA acts as the control centre for fear response activation and inhibition, either directly or indirectly at the level of the CMA as exerted by the OFC (van Honk, Terburg, Thornton, Stein, & Morgan, 2016).

Total amygdala damage results in the impaired recognition of fearful facial expressions, an innate threat cue in humans, as demonstrated with SM046 (Adolphs R. , Tranel, Damasio, & Damasio, 1994). Although this finding was due to her inability to unintentionally fixate on the eye region of faces (Adolphs, et al., 2005), it still leaves the question unanswered about the exact mechanism of amygdala subregional responses to innate threat cues (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). In contrast to SM046, the Namaqualand UWD patients seem to have a strong predisposition for fear, given the abnormally high prevalence of anxiety disorders within this population (Thornton, et al., 2008). These disparate findings led van Honk and colleagues to investigate the ability of the Namaqualand cohort to recognise and process innate fear stimuli, so as

to translate rodent findings and to support previous work of the specific role of the human BLA in innate threat (van Honk, Terburg, Thornton, Stein, & Morgan, 2016; Terburg, et al., 2012).

The results from an emotion-recognition task showed that UWD participants outperformed the controls in full-blown fear recognition with longer fixation on the eyes of fearful faces than control subjects (Terburg, et al., 2012). A hypervigilance for fear was one hypothesis that could explain the hyperfixation on the eyes of selectively fearful faces. Fear hypervigilance can be investigated unconsciously with an emotional Stroop task, as is often done in individuals with fear disorders (van Honk, Peper, & Schutter, 2005). The UWD individuals convincingly demonstrated fear hypervigilance in a backward-masked unconscious emotional Stroop colour-naming task, as they exhibited slower colour naming after the subliminal presentation of fearful faces (Terburg, et al., 2012). Their findings correspond with rodent research suggesting the BLA regulates innate and acute fear responses by inhibiting an overreactive fear response by the CMA to mild threats (Graeff & Del-Ben, 2008; Macedo, Cuadra, Molina, & Brandão, 2005; Martinez, de Oliveira, & Brandão, 2007; Tye, et al., 2011).

This interpretation does not address the question of where the CMA might receive the sensory input to produce these hypervigilant fear responses from, if not from the BLA? One explanation is that, as a usual contributor to sensory information processing, the role of the BLA to interpret fear information may have been reassigned to the OFC and superficial amygdala (SFA) by means of neuroplasticity (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). Another explanation could be that the nature of the calcifications, being progressive with age, could exclude some regions of the BLA that are specifically involved in sensory transfer between the CMA and BLA. Rodent studies have however suggested that different mechanisms within the BLA are responsible for the fear response and sensory input respectively (Mobbs, et al., 2007).

Together with the results from SM046, which indicated a hypovigilance for fear after BLA and CMA damage, the findings from the Namaqualand UWD population suggest that BLA damage results in

hypervigilance for fear. These findings provide a foundation for the translation of rodent BLA studies on the serial amygdala processing model (van Honk, Terburg, Thornton, Stein, & Morgan, 2016). Future research is warranted in this population of UWD individuals in order to gain more insights into the serial processing hypothesis of the BLA.

Processing conflicting social stimuli

In non-threatening conditions, the Namaqualand UWD cohort exhibited paradoxical facilitation of working memory (Morgan, Terburg, Thornton, Stein, & van Honk, 2012), but they exhibited hypervigilant responses to mild threat cues in an emotional Stroop interference of backward-masked fearful expressions (Terburg, et al., 2012). This led to de Gelder and colleagues hypothesising that this group of BLA damaged individuals would be impaired in processing behavioural information, especially in the presence of conflicting tasks. Using the "face-body compound task" that exploits the phenomena of emotionally conflicting information when a facial expression does not match the body language (Meeren, van Heijnsbergen, & de Gelder, 2005), de Gelder and colleagues investigated whether BLA damage would indeed result in the processing of emotionally conflicting information.

Their hypothesis was confirmed when the UWD group had profound impairments in processing emotionally conflicting information when the facial expression did not match the body language (de Gelder, et al., 2014). No differences in fear recognition were found between UWD and control groups. Data from the eye-tracking device showed that, even though they fixated predominantly on the faces, UWD participants still had severe difficulty identifying emotional expressions when bodily emotion conflicted that of the facial emotion. The inability of these participants to ignore task-irrelevant threatening body language, solidifies the concept that the dysfunctional BLA allows for inappropriate fear responses to mildly threatening stimuli in the absence of inhibitory regulation of the CMA (de Gelder, et al., 2014; van Honk, Terburg, Thornton, Stein, & Morgan, 2016; Koen, et al., 2016).

Economic behaviour

The brain's reward system, of which the NAc is a major component, is a strong driving force behind motivated economic behaviours in humans and rodents (Floresco & Tse, 2007) (Ghods-Sharifi, St.Onge, & Floresco, 2009). The BLA acts directly, and indirectly via the OFC, on the NAc to subserve instrumental economic behaviours that are selfish and rational, as implied by amygdala parallel processing models in rodent research. Contrary to the role of the BLA in parallel processing, the CMA promotes affective economic behaviours that are irrational and impulsive (Balleine & Killcross, 2006; Bos, Brummelman, & Terburg, 2015; van Honk, Terburg, Thornton, Stein, & Morgan, 2016). These distinct functions of the amygdala subregions conform to the classical and contemporary economic models respectively. Neuroimaging studies have however shown that the valence of economic behaviour (rational or impulsive) is determined by the mutual processing of the amygdala together with the NAc (Haruno, Kimura, & Frith, 2014).

To determine whether the rodent parallel processing model also applies to humans, van Honk and colleagues performed neuroeconomic research on the Namaqualand UWD cohort using a trust game. During this paradigm, varying investments towards others can be either rational (instrumental) or affective (impulsive) in expectation of subsequent returns (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013). The results indicated that BLA damaged individuals made close to 100% larger investments to anonymous trustees. The significant difference between investments of UWD participants and controls was not present during a risk task in the form of a lottery. In fact, BLA damaged individuals even made slightly less risky decisions in the risk paradigm. This indicates that the difference in investments to trustees between UWD and controls was a result of the social aspect of the trust game, and not risky behaviour. To control for social naivety, participants reported their expectations about returns from trustees, and no difference was found between UWD and controls. UWD participants were also not able to rationalise their high investments to trustees, which indicates that their behaviour is based upon impulsive-affective choice. No difference was found between UWD and controls' facial trustworthiness ratings of others, again supporting the

notion that the generous economic investments made by UWD participants are altruistic and driven by the CMA in the absence of a functioning BLA (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013).

Further neuroimaging investigations are required to elucidate these findings, however, a recent follow-up study aimed to gain insights into the role of social learning in economic behaviour without a BLA. The findings of this study, as well as others on learning in the Namaqualand UWD population, are discussed next.

BLA's role in learning

Rodent research has established the role of the BLA in learning processes as a reinforcer and suppressor of behaviour by forming action-outcome associations (Hernandez-Lallement, van Wingerden, Schäble, & Kalenscher, 2016; Chesworth & Corbit, 2017). The rodent BLA encodes values of outcomes in social experiential learning and allows for behavioural adjustment following positive or negative feedback from partner rats (Hernandez-Lallement, van Wingerden, Schäble, & Kalenscher, 2016). Very little is known about the human BLA in social learning, given the challenges of isolating the BLA as a region of interest in human research. With a previous cross-species study on the BLA between rodents and humans, Terburg and colleagues demonstrated that rodent amygdala models of escape behaviour from imminent threats directly translates to humans (Terburg, et al., 2018). These defensive behaviour mechanisms, mediated by the BLA, have been evolutionary conserved across humans and rodents, which prompted further research to attempt translating the rodent BLA framework of social experiential learning to humans.

Rosenberger and colleagues hypothesized that the rat BLA's role in experiential social learning would be mirrored by the function of the human BLA. They presented the Namaqualand UWD cohort (n=5) and healthy matched controls (n=17) with a repeated trust game, in which participants had to make a series of sequential investment decisions to unknown co-players before receiving generous or selfish back-transfers from these trustworthy or untrustworthy trustees. Their findings showed that

controls were able to successfully learn which trustee to trust, based on their reciprocal behaviour, whereas UWD participants were unable to learn to adapt their investment behaviour (Rosenberger, et al., 2019). Control participants earned significantly more in this investment paradigm than UWD's, pointing to the absence of experiential social learning in BLA damaged individuals. BLA-damaged participants were also unable to distinguish between the trustworthy and untrustworthy players when asked to rate the trustworthiness of the trustees. In contrast, controls made trustworthiness ratings that corresponded well with the behaviour of the respective trustees.

The researchers concluded that rodent models of social experiential learning translate to humans, and that the human BLA plays an important role in learning about and adapting to others' trustworthiness (Rosenberger, et al., 2019). Further behavioural and imaging studies are needed to investigate the extent to which the human BLA is involved in separate learning processes.

1.4 Social and economic decision-making

Decision-making occurs when an organism evaluates the value of two or more options, thereby taking the appropriate course of action to achieve or obtain the most desirable results as predicted during contemplation. The ability of humans to choose an optimal course of action from multiple alternatives presented to them has been investigated across various disciplines using a diverse range of measurement techniques. Different approaches in decision-making research from psychology, neuroscience and economics have resulted in a lack of integration between findings in these modalities, leaving gaps in our understanding of this complex process. The introduction of neuroeconomics as an interdisciplinary field has brought some cohesion between previously distinct disciplines (Camerer, Loewenstein, & Prelec, 2004).

Complex sets of processes converge across various brain systems to allow for optimal decision making. Before we take a closer look at some of these processes, we can first simplify the decision-making procedure itself by dividing it into three basic stages (Paulus, 2007):

a) The assessment stage. During this stage, all possible outcomes or options are evaluated, considered and a preference between these options is generated.
b) The action stage. After considering which alternative would be the most ideal, action must be taken to either execute or inhibit this action.
c) The evaluation stage. After a decision has been made, the outcome of that choice is experienced and evaluated.

The orchestration of neural systems involved in the different stages of decision making is not well understood in humans due to limitations of research methodologies to safely validate intra-regional communication. Apart from the amygdala and its subregions, most research on decision-making has identified the following neural structures as important role players in this mechanism: striatum, orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex and the somatosensory cortex (Bechara & Damasio, 2005; Gupta, Koscik, Bechara, & Tranel, 2011; Cardinal & Howes, 2005; Chang, et al., 2015; Ghods-Sharifi, St.Onge, & Floresco, 2009). These brain regions, most commonly activated during studies of social and economic decision-making, are briefly described below and illustrated in figure 4.

The striatum and its subcomponents play an important role in processing reward. As a major site for dopaminergic projection in the mesolimbic dopamine system, the striatum is especially involved in decision-making of a social nature (Sanfey, 2007) during delivery, anticipation and prediction of awards. Patients with mood disorders often present with challenges of assigning values to different outcomes when making decisions, which is due to abnormalities in the ventral striatum (Paulus, 2007).

There have been wide discrepancies between animal and human findings on OFC function, but more recent work found that it is critical for value-based decision-making (Wallis, 2012). The OFC assigns value to alternatives and subsequently determines the most ideal choice. With its strong bidirectional connections to the BLA, the OFC identifies and utilises the motivational significance of

cues (Fellows L. K., 2007). As the BLA and OFC compete for resources, a decline in activity within the BLA may result in hyperactivation in the OFC. Along with the OFC, the ventromedial prefrontal cortex (vmPFC) plays an important role in reinforcement learning and decision-making as a value representor (Fellows & Farah, 2007). Patients with lesions to the vmPFC lack social judgement and tend to make irrational decisions (Koenigs & Tranel, 2007).

The anterior cingulate cortex is considered a convergent hub between motivation, cognition and action (Bush, et al., 2002). This region subserves the performance of novel tasks, error-processing and reward-based decision-making (Bush, et al., 2002). The ability of humans to learn how to benefit others in social decision-making is also underpinned by the ACC, making it a special region of interest in social decision-making as well as reinforcement learning (Lockwood, Apps, Valton, Viding, & Roiser, 2016).

Considering the neural substrates of decision-making in broader terms, the subjective value of decisions is present in restricted neural regions where information from subcortical and dorsal regions integrates. As seen in preference judging paradigms, value-based decision-making is disrupted following damage to the OFC or vmPFC (Fellows & Farah, 2007; Henri-Bhargava, Simioni, & Fellows, 2012). Reward learning is distorted by striatal dysfunction, as caused by Parkinson's disease, or damage to the striatum (Clark, Cools, & Robbins, 2004). Electrophysiological research in rodents and primates indicates that decisions of an intuitive nature are subserved by limbic interactions between the amygdala and ventral striatum (Bechara A. , Damasio, Tranel, & Damasio, 1997).Decision-making often requires explicit recall of preceding experiences in order to make predictions of future outcomes. This recall-prediction is dependent on the hippocampal-vmPFC interplay supported by thalamic visual-attentional processes in OFC-vmPFC interactions (Rudebeck & Murray, 2014). Neuromodulatory systems are considered central to temporal task models of decision-making (Dagher & Robbins, 2009). An example of such a system would be the dopaminergic signals crucial for associated learning between expected and actual rewards. These dopaminergic

mechanisms are especially relevant in research on the negative effects of substance abuse on decision-making (Cohen & Aston-Jones, 2005).

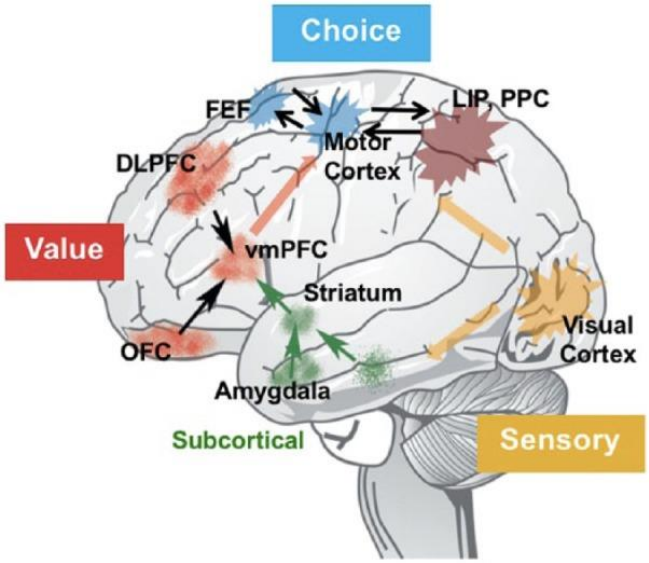

Figure 4: Schematic representation of a suggested decision-making network with its main neural components within the human brain. (Chawla & Miyapuram, 2018)

Economic decisions are mostly self-serving and instrumental, according to classic economic models (Hollis & Nell, 1975). Humans will mostly make selfish, goal-directed decisions for themselves if costs and gains are involved. However, modern economical models have added that economic decisions, especially social-economic decisions, can be impulsive and affective (Fehr & Camerer, 2007) when influenced by theory of mind, empathy traits and emotion recognition. Instrumental behaviours are dependent on the BLA, as the valence of a possible outcome must be determined and constant feedback is required in order to make these evaluations (Ghods-Sharifi, St.Onge, & Floresco, 2009). Efferent projections from the BLA to the sensory cortical areas provide a mechanism for this feedback by forming cue-outcome predictions (Kapp, Whalen, Supple, & Pascoe, 1992). Conditioned responses may be mediated by the CMA through its afferents to the brainstem and midbrain. The CMA also receives information from the BLA regarding the valence of stimuli (Gupta, Koscik, Bechara, & Tranel, 2011).

Experimental decision-making paradigms in humans usually involve monetary gambles or a choice between two stimuli with respective attributes/values (Rilling & Sanfey, 2011). These same paradigms can also be applied to social decision-making with the simple addition of a choice factor dependent on the reaction of another individual. Most decision-making studies are in the form of a Game Theory task from experimental economics. These include the Trust Game, where an individual has to decide on an endowment to invest in a stranger. The stranger can then either reciprocate the transaction or keep everything for themselves (Camerer, 2003). Similarly, the Prisoners Dilemma game allows for the same procedure, only both players make their decisions simultaneously. The Ultimatum game is used to evaluate the response to resource allocation on the responders' behalf (Henrich, et al., 2006) . Lastly, the Dictator Game gives full control to one player, with the other simply being observant and a passive receiver (Camerer, 2003). These tasks are different from the task utilised in this experiment. For this thesis, a simple reinforcement learning task was employed to uncover possible attributes of specific neural regions. This task requires less punitive behaviour from participants, as it is difficult to keep conscious tabs of the rate of learning for oneself versus another (Lockwood, Apps, Valton, Viding, & Roiser, 2016).

Reinforcement learning has been investigated in humans using fMRI, which has aided in identifying the neural structures central to decision making. Consistently higher activation of the ventral striatum, the ACC and the dorsolateral PFC exist during decision-making (Lockwood, Apps, Valton, Viding, & Roiser, 2016; Rilling & Sanfey, 2011) (Lee & Seo, 2016). With the prominent projections between the BLA and these structures, some adaptations of neural mechanisms can be expected in individuals with UWD. A possibility exists that a previous finding in this cohort, namely paradoxical facilitation of working memory in patients with BLA lesions, could alter the results of the reinforcement learning task (Morgan, Terburg, Thornton, Stein, & van Honk, 2012).

1.5 Research Gaps

There has been limited research into the human BLA and its unique contribution to social and economic decision-making. The studies that have been conducted on the human BLA mostly used neuroimaging methods, which often lack the ability to identify whether neural activation is indeed associated with a specific function (Sanfey, 2007). For this reason, neuroimaging is not sufficient when translating research from efficiently investigated animal models, often including paradigms such as lesion methods and pharmacological inactivation of specific regions of interest.

Previous work on this same group of UWD participants found that they had decreased ability to learn probabilities between stimuli and their predictive ques during fear-conditioned learning (Klumpers, Morgan, Terburg, Stein, & van Honk, Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage, 2015), however we are not sure how these BLA lesioned individuals would learn probabilities in an economic paradigm. A recent study was undertaken to translate rodent findings of the BLA's role in social experiential learning (Rosenberger, et al., 2019), yet this finding emphasised the ability of the BLA to adjust to feedback from others, whereas questions about unreciprocated choices have not been investigated.

Although BLA damaged individuals are considered altruistic when making explicit social-economic choices (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013), it is unknown whether they would show a similar pattern of choice when the decision-making process occurs on a more subconscious level, such as performance during reinforcement learning. Many studies on economic decision-making involve aversive components such as high risk or delayed discounting, whereas research on the structures involved in simple, self-beneficial economic decisions without major risks or penalties, has been neglected. The human amygdala has been implicated in emotional processing (Bechara A. , Damasio, Damasio, & Lee, 1999; Bechara A. , Damasio, Tranel, & Damasio, 1997), which could be an

important factor in social decision-making, however none of these studies looked at the subregional contributions of the amygdala to emotional information in decision-making.

2. Rationale

The neural processes involved in decision-making, such as memory, learning, value predictions, affective considerations, risk and reward, are considered important aspects of cognition. Discoveries about the mechanisms involved in these aspects have already made valuable contributions to our current understanding of both functional and dysfunctional human behaviour. Yet, information about the exact role of specific brain regions in these processes are lacking. Understanding the implications of our decisions on others and also that of others' decisions on us, is relevant on all levels of human interaction: from the implementation of public policies to the most intimate interpersonal exchanges (Sanfey, 2007). Furthermore, understanding the mechanisms and roles of neural regions involved in decision-making, and how these become dysfunctional, creates important opportunities for decision-making research to contribute to our understanding of, amongst others, mental disorders with impaired decision-making (Paulus, 2007).

A compelling body of evidence exists from rodent research outlining the role of specific amygdala subregions in social and affective behaviour, however these findings have not been translated to humans. Intra-structural interactions are poorly understood because of the challenges faced when studying these interactions in humans: the inability to study these structures as individual, isolated regions. Neural activations, as measured by neuroimaging, do not necessarily indicate the role of other regions associated with that activity (Sanfey, 2007). Lesion studies can overcome this hurdle and offer insights into the unique function of specific brain regions under specific conditions.

The purpose of this study is to determine whether the human BLA is required for adapting the value of stimuli during economic decision-making in a reinforcement learning paradigm. In an attempt to replicate previous findings of altruism in BLA damaged individuals (Van Honk, Eisenegger, Terburg,

Stein, & Morgan, 2013), I also wanted to investigate whether BLA lesions in humans would result in more prosocial choices in a social reinforcement task.

Salience and threat detection through social-emotional regulation has been attributed to the BLA (Koen, et al., 2016). Given the BLA's rich interconnectivity with regions of the brain associated with decision making (PFC, NAc, OFC), altered decision-making behaviour is expected in patients with BLA damage. Due to the high selectivity of bilateral BLA lesions in the UWD patients in our sample group, we can perform research on humans that would not be possible otherwise. This rare research opportunity has already proven to not only deepen our understanding of the human BLA, but has also provided outcomes that contribute to our knowledge of disorders of fear and aggression (Koen, et al., 2016; de Gelder, et al., 2014; Hortensius, 2016; Klumpers, Morgan, Terburg, Stein, & van Honk, 2015; Terburg, et al., 2012; van Honk, Terburg, Thornton, Stein, & Morgan, 2016; Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013).

2.1 Research questions

By investigating decision making in humans with selective bilateral BLA lesions, I wanted to answer two questions:

1. Will UWD patients be impaired in making self-beneficial decisions that involve monetary gains and losses in a non-social reinforcement learning task?
2. Will BLA lesions result in increased social learning through prosocial decision making in a probabilistic reinforcement task?

2.2 Hypotheses

For each of the abovementioned questions, the following hypotheses were proposed:

1. BLA damaged patients will not be impaired in non-social reinforcement learning.
2. BLA damaged patients will present increased social learning and make more pro-social economic decisions to benefit strangers.

2.3 Aims

By investigating decision making in patients with UWD, I aimed to translate rodent BLA findings of decision making to humans.

I aimed to determine whether selective BLA damage in humans impairs instrumental non-social economic decision-making. This was achieved by first looking at non-social reinforcement learning that involves monetary gains and losses.

I also wanted to investigate whether BLA lesions lead to altered behaviour in social decisions, specifically altruistic decisions relating to monetary gains.

3. Methods

3.1 Design and setting

I used a behavioural computer-based task examining the effect of bilateral basolateral amygdala damage (independent variable) on social and economic decision-making (dependent variables). To achieve this, the choices made by participants with UWD in a probabilistic reinforcement task were compared to those of healthy matched-controls in different scenarios.

This research took place at Daisy Country Lodge, an ideally located and well-known establishment in Springbok, Northern Cape since all participants are familiar with it as the testing location for the past few years. An open-plan accommodation unit was converted into a research lab, ensuring privacy for each participant as well as adequate lighting, ventilation and resting facilities. The close proximity of the research facility to the residences of participants ensured a comfortable and familiar setting in which the tasks were performed. Participants were also familiar with the investigating student, who has been facilitating the research since 2015. The data analysis was also conducted in Springbok, Northern Cape.

The computer-based behavioural tasks were originally developed and conceptualised in English, therefore translation thereof to the mother tongue of the participants was required. These computer-based tasks were thus translated to Afrikaans by the investigating student, a fully bilingual local inhabitant of Namaqualand, where the participants also reside. This ensured that the translations were not only made into the participants' mother tongue of Afrikaans, but also in the specific dialect unique to Namaqualand. Semantic equivalence has been ensured by doing a pre-study test with participants who had to explain their understanding of the translated tests. Participants' results in the pre-study test served as a clear indication of whether the test was understood and whether it still maintained its semantic equivalence.

Great care was taken during the translating process that all concepts were made clear and understandable. The pre-study test also provided an opportunity to make amendments, should they have been deemed necessary. This, however, was not necessary as semantic equivalence was maintained.

3.2 Sample

The sample comprised of six participants with UWD and twenty matched, healthy controls. Control participants were matched for age, gender, demographic area, income class and intelligence based on the Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011), which provides reliable measures of intelligence for non-Westernised citizens from developing countries. UWD participants were included based on a clinical diagnosis of UWD which has previously been confirmed with genetic testing and MRI scans showing selective bilateral BLA damage. Participants were included if they resided in the Namaqualand region, a demographic area stretching from the North-Western regions of the Western Cape, to the North-Western regions of the Northern Cape. Female participants aged 27-69 years were included. Exclusion criteria for this study were: signs or proof of cognitive impairments, psychopathology or severe health complications other than UWD.

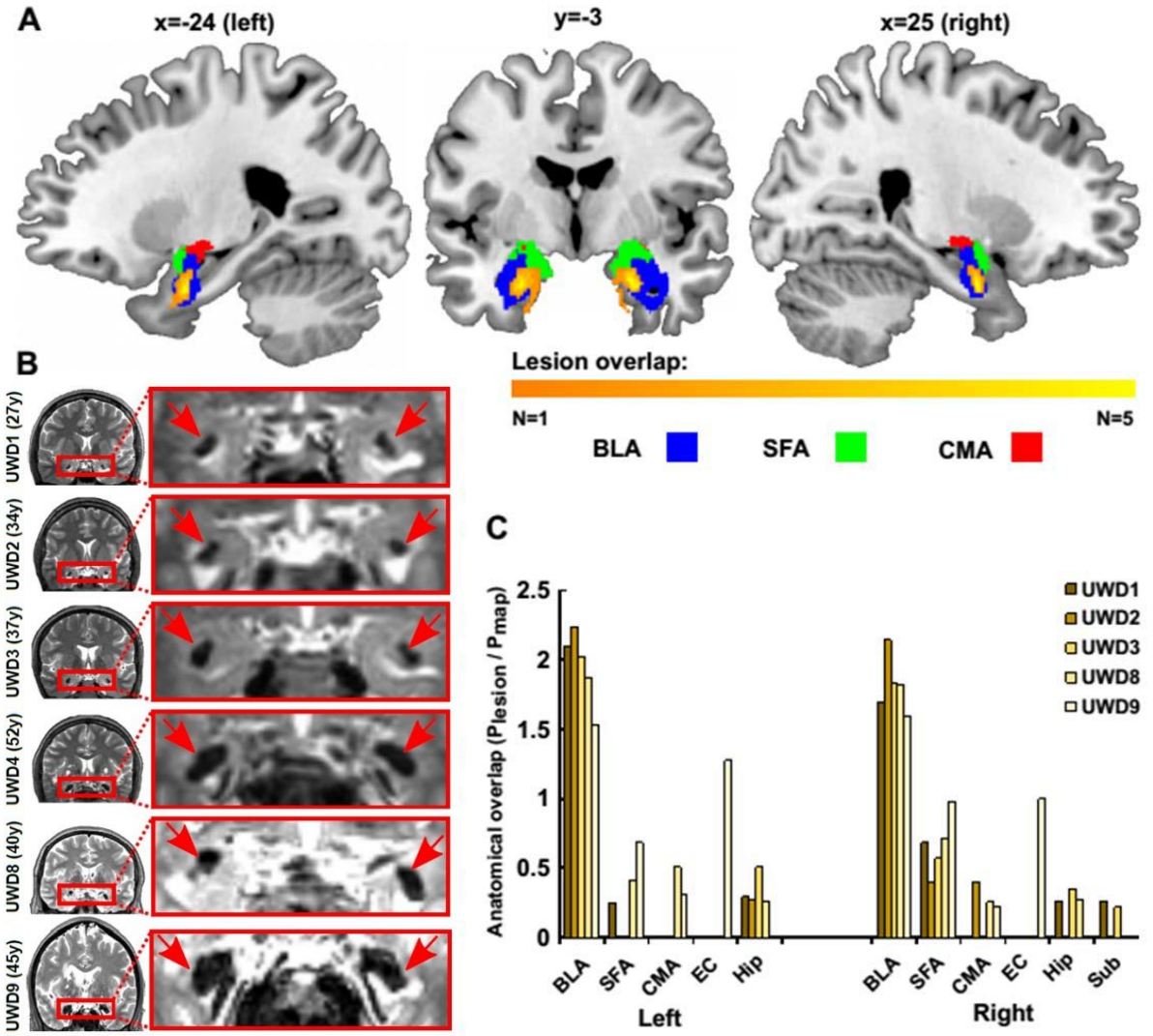

*Figure 5: Imaging findings from the UWD Namaqualand cohort: **A**: Lesion-superimposition in MNI Space plotted within the subregions of the amygdala showing overlap probability of >50%. **B**: T2-Weighted MRI scans showing progressive focal bilateral lesions in the BLA. **C:** Bar-graph of P(excess) values, indicating volumetric and anatomical lesion overlapping (>1 indicates a reliable overlap). (Terburg, et al., 2012; Rosenberger, et al., 2019)*

All participants were recruited from an existing pool of volunteers and patients involved in the overhead study on UWD (HREC Ref 639/2016, see appendix 8.3). Originally, these patients were recruited from clinics in Namaqualand and control participants were recruited by word of mouth from within the same communities. Staff at local clinics were made aware of the clinical features of possible UWD patients (hoarse voice, skin lesions) by the principle investigators in the past. When the staff at these clinics happen to treat or notice patients with possible symptoms, they informed the PI whom then contacted the potential participant. During the recruitment process (by word of

mouth and through clinics) control participants were selected based on their socio-demographic circumstances, i.e. They are inhabitants of Namaqualand, female, fall within the selected age group and fall within a low-income group. Since their social-demographic information qualified them for possible participation initially, the use of a measurement instrument to further confirm their eligibility was not been considered necessary for this specific study.

The uniqueness of the culture in the isolated communities in Namaqualand is a strong influence on the social interactions of inhabitants. Demographic-specific poverty influences the individuals' perception of monetary value, a key focus in economic decision-making. It was therefore important to use matched controls.

3.3 Measurement Instrument

3.3.1 Probabilistic reinforcement task

Developed using Ztree version 3.6.7 software.

I used an adapted reinforcement-learning task to test economic reinforcement learning (Eisenegger, et al., 2014) as well as social reinforcement learning (Lockwood, Apps, Valton, Viding, & Roiser, 2016). Participants performed a probabilistic reinforcement learning task where they were required make decisions based on the learned probability that one of two symbols could result in monetary reward or loss. These two symbol pairs were represented by Chinese symbols with distinct individual features. One pair was associated with monetary gains (a probability of 75% to win R3 or a probability of 25% to win nothing), and a second pair was associated with a loss (a probability of 75% to lose -R3 or a probability of 25% to lose nothing). Participants performed this task in two different learning contexts: self and prosocial. Participants were instructed that when they are playing for themselves, they will receive any money won. When they were playing for the other person, that participant would receive the money. The "other participant" was in fact fictitious and no real

participants were involved. Participants were informed that the other participant is not aware that they are performing a task where they could earn extra money, and that any money they win for this person will be given to the other participant anonymously.

3.4 Research team

All tasks and contact with participants occurred through the investigating student, who also collected the data and conducted the statistical analysis. I facilitated the experiments throughout the study to ensure continuity. I am a member of the same community as the participants, speak the same language as the participants, and they are comfortable and familiar with me, having acted as a research facilitator previously. The satellite research laboratory setup was overseen by Professor Jack van Honk.

3.5 Procedure

Upon their arrival at the test facility, all participants were given a light, healthy breakfast and enough water to stay hydrated. They were then briefed on the events to take place and the timeframe. Each participant was assigned a unique numerical ID for the day and they were divided into groups of 4 – 6 individuals who entered the lab at a time. This ensured that each participant had enough room for privacy and that individual attention could be given to participants should they experience any difficulties. When individuals were not in the lab busy with the experimental procedure, they were given freedom to relax at their own leisure on the premises of the lodge until their group was called for testing.

3.5.1 Preliminary stage

The procedure was initially explained to the participants by the investigating student in a classroom-style setting. Printed screenshots of the behavioural task were used to prepare the participants adequately. With each participant sitting in front of their respective screens, they then read the detailed instructions along with the investigating student as it appeared on the screen. Following this, all participants simultaneously watched a simulated play-through of the procedure. Any

questions were answered thereafter. Participants were asked to fill in control questions that test whether they comprehend the task, before doing an interactive practice run. In this practice run, self-blocks began with the instruction “play for yourself” and the word “you” was written above all choice symbols and outcomes. Prosocial blocks began with the instruction “Play for the other person” and the words “Other person” was written above all choice symbols and outcomes. This ensured that participants were explicitly aware whether they were making decisions for themselves or for another participant. Participants did this practice run of one block of the task in a separate session after the simulated session to familiarize themselves with the experimental task and the keys on the computer associated with their choices. During this practice they were instructed that the outcomes of the practise rounds would not be converted into any payment.

After all the participants performed at a fully competent level in the control questions as well as the practice round, the actual task commenced.

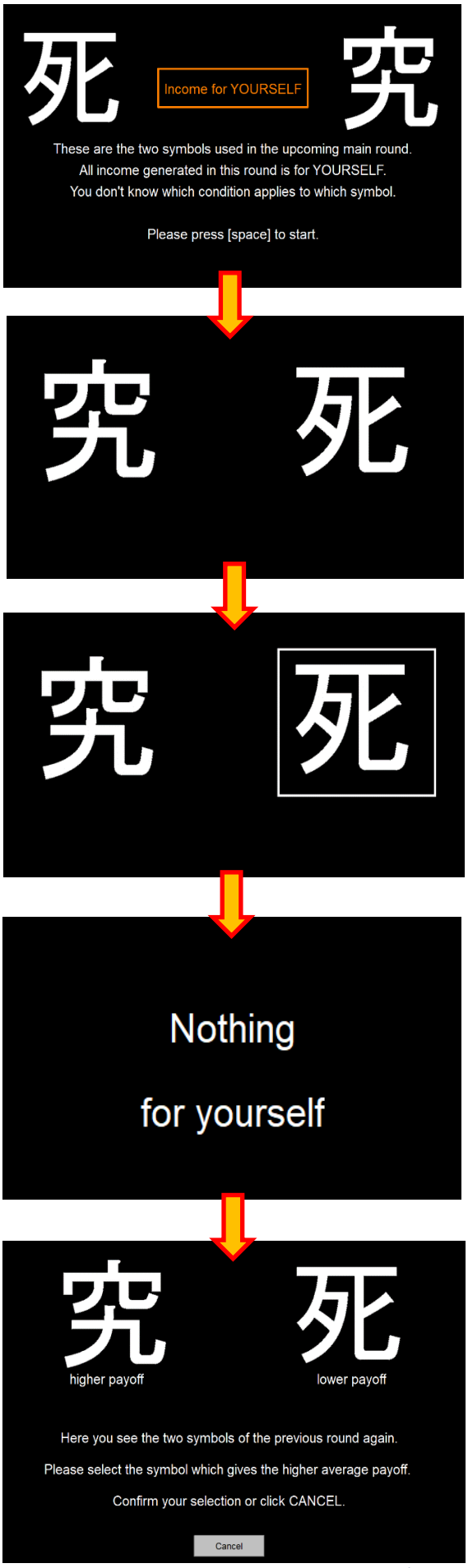

Figure 6: Screenshots of trial structure and procedure. Condition (Yourself/Other player) clearly indicated. (English version)

3.5.2 Data collection stage

On the first screen, the phrase “play for yourself” or “play for someone else” appeared. The participants saw two symbols on their screen, of which they had to choose any one they prefer. After a few trials, participants began to recognize the pair of symbols associated with gains and with losses respectively.

The total earnings from this task were automatically calculated by the software and the amount was paid out to them in cash at the end of all the tasks. Throughout the entire process, I remained in the same room as the participants should they have required assistance, however still remaining out of sight so that they did not feel as if they were being watched.

Trial structure:

Each block began with an instruction screen that indicated who would receive the outcomes (Self or Other participant) for 2 seconds. This was followed by the presentation of two abstract stimuli for 3 seconds during which participants were required to select one. These stimuli were in the form of plain Chinese symbols in white font on a black background. If no response was indicated during this time, the words “too late” appeared in red on the screen. The selected option was shown for 300 ms, followed by a delay (2,5 seconds), then the outcome of their choice (+R3/ nothing /-R3). The side of the screen on which the two symbols appeared was counterbalanced so that participants could not perform action-based learning. They were instructed that the stimulus’ location on the screen does not matter, to encourage them not to learn based upon the motoric action they had performed but to learn the contingencies between the stimuli regardless of position and outcome.

Each participant did 192 trials in total, 48 for self-win (Self Gain), 48 self-loss (Self Loss), 48 prosocial win (Other Gain), and 48 prosocial loss (Other Loss), presented in 12 blocks of 16 trials. Blocks were presented in pseudorandom order, with the same block type never presented twice in a row.

3.6 Ethical considerations

The vulnerability of our participant population has been acknowledged and was kept in mind at all times.

Before commencement of this study, ethics approval had been given to the overhead study with HREC ref 639/2016 (See Appendix 8.3), however approval was obtained from the University of Cape Town Human Research Ethics Committee (HREC) for this specific study for degree purposes with the HREC reference 740/2017 (Appendix 8.3). Because this study formed part of the overhead project, an expedited review was requested and granted. Data and all appropriate documentation were securely stored after the completion of the study. UCT holds a non-negligent harm insurance policy which applies to this study.

UWD patients and control participants were given similar informed consent forms in their mother tongue, Afrikaans, which detailed the research to be conducted in lay terms. English translations of these forms can be found in appendix 8.4. Each participant gave their written and verbal consent to take part in this study only after a full explanation had been given, studies described fully and time for personal consideration had been given. Signed participant consent was obtained and the right of the participant to refuse to participate without giving reasons was respected. All participants were free to withdraw at any time from the study without giving reasons and without prejudicing further participation.

In compliance with data protection legislation, the confidentiality of participants was preserved. During the entire study, the research team strove towards obtaining anonymity of participants by assigning each with a unique RIN code, which was kept separate in a secure digital file at all times. All laptops and computers used in the research are under password protection.

Importantly the research team was aware that, because of the symptoms of UWD, the rarity of the disease and the small recruitment area, participants may possibly be identifiable after publication or

release of this thesis. However, this can only link individuals to possible participation in the study, and no direct results refer to one participant in person. Results have been reported for the group and not for individuals.

At the close of the experiment, participants were reimbursed with a flat fee for their participation. In addition, they won a limited variable amount based on their decisions in the decision-making paradigm. Monetary incentives are key components of decision-making paradigms, and only by adding an incentive contingent on decisions are we able to assume validity of the dependent measures. The amount of pay-out received by individuals was determined by their performance in the decision-making paradigm, which left no room for undue inducement.

All research-related costs were compensated for, including travel, child care and absence from occupational responsibilities.

The nature of the tasks (computer based behavioural tasks) did not pose any risks to participants, and these tasks actually proved to be quite enjoyable to the participants. No possible ethically controversial issues were identified.

Over and above the regular HREC confidentiality and consent regulations, I recognised that the study population, UWD participants in particular but also healthy controls, constitute an especially vulnerable demographic by virtue of gender, historical race-based disadvantage, economic hardship, and in the case of the UWD participants, stigma and disability associated with cosmetic skin lesions and profound hoarseness of voice. Through care and sensitivity to these factors, the research team has established an enduring relationship of trust with all participants and every care has been taken to maintain this trust during the course of this research.

3.7 Data Analysis

IBM SPSS version 25 and Microsoft Excel 2016 was used to do the initial summary and preparation of the raw data. IBM SPSS version 25 was used to analyse the data by means of visual representations,

seen in the line graphs and bar graphs. A random effects Generalised Least Squares regression was conducted using Stata 15.1. Fixed effects (within) and between-effects interacted to produce coefficients. The individual ID's (RIN) of each participant was used as the group variable. The outcome variable was the correct choices made. The participant status (control or UWD) was the within-subject variable and the domain (Gain or Loss) acted as the predictor variable. The data file was then split by the condition (playing for Self or playing for Other) as an "if" condition. The predictor variable and the "if" condition bartered, so that all the between-subject variables could be accounted for.

3.7.1 Data safety, storage and protection

All data was gathered by the investigating student and stored under password protection on a personal laptop. Data was also saved to an external hard drive, which was stored securely.

Participants were assigned a unique Research Identification Number (RIN) to ensure anonymity. No personal identifiers were linked to information, and documents that do contain the names of participants are kept separate from their RIN files. Only the investigating student and two supervisors have access to these files. Participants' names will never appear in any reports resulting from the project and all analyses were conducted solely by RIN. The data will be kept for a minimum of 5 years under password protection.

4. Results

Table 1: Demographic data matched for age, gender and occupational status.

	UWD (n=6)								Controls (n=20)	
	UWD1	**UWD2**	**UWD3**	**UWD8**	**UWD9**	**UWD4**	**Mean**	**SD**	**Mean**	**SD**
Age	32	39	43	39	47	58	43	6,33	42,05	
							Number(%)		**Number(%)**	
Unemployed	0	0	1	1	0	1	3(50)		9(45)	
Part time/full employed	1	1	0	0	1	0	3(50)		11(55)	

The final group of research participants comprised six female patients with clinically confirmed UWD, aged between 32 years and 58 years (M=43; SD=6,33) and with Full Scale Intelligence Quotient (FSIQ) scores ranging between 81 and 97 (M=87.83 SD=5.45) (Rosenberger, et al., 2019). The control group comprised 20 healthy females aged between 27 and 67 years (M=42,05; SD=9,49). Results from all participants were included in the analysis.

Table 2: Results from previous research for UWD participants in the Wechsler Abbreviated Scale of Intelligence (WASI) for visual IQ (VIQ), performance IQ (PIQ) and full-scale IQ (FSIQ). (Rosenberger, et al., 2019)*

*Results for UWD4 were initially omitted due to concerns about her comprehension of tasks

	UWD1	**UWD2**	**UWD3**	**UWD8**	**UWD9**	**Mean**	**SD**
VIQ	97	84	93	89	87	90	5.1
PIQ	99	87	85	95	89	91	5.83
FSIQ	98	84	84	91	86	89.2	5.54

In previous years, one of the UWD patients (the eldest amongst UWD participants) had to be excluded due to difficulty in comprehending tasks. It was previously believed that her age might have played a role in her difficulty to understand tasks, as her limited exposure to technology and digital media could have rendered her completely new to modern concepts such as typing, reading on-screen instructions, or interacting with a technological device. This was however resolved by facilitation of the research by the investigating student, who was able to both communicate with her in her mother tongue and dialect. The student facilitator also paid special attention to this individual to ensure she followed instructions well, interacted accordingly with technological devices, and understood the tasks sufficiently.

To determine whether selective BLA damage in humans impairs instrumental non-social economic decision-making, I first looked at non-social reinforcement learning which involves monetary gains and losses. Participants made a series of decisions for themselves that resulted in either gains or losses. To get a clear indication of differences between UWD and controls, both between domains and between conditions as well as intra- and inter-level differences, a Generalised Least Squares (GLS) random-effects model was used for statistical analysis. The model provided interactions on all levels and from every perspective, ensuring a thorough comparison. Each domain and condition were investigated individually in relation to the others.

*Table 3: Summarised coefficients (percentage point differences) from results of the GLS random-effects model, as shown per domain (Loss or Gain) and condition (Self or Other). Parentheses indicate standard errors. Symbols indicating level of significance: + p<0.10, * p<0.05, ** p<0.010*

	SELF only	OTHER only	GAIN only	LOSS only	All interactions
Indicator for UWD participants	-0.02	-0.00	-0.02	0.10	-0.02
	(0.07)	(0.07)	(0.08)	(0.07)	(0.07)
Indicator for Loss domain	-0.13	0.04			-0.13
	(0.02)**	(0.02)+			(0.02)**
UWD participants * Loss domain	0.13	0.05			0.13
	(0.04)**	(0.05)			(0.05)**
Indicator for other condition			-0.17	0.00	-0.17
			(0.02)**	(0.02)	(0.02)**
UWD participants * other condition			0.02	-0.06	0.02
			(0.04)	(0.05)	(0.04)
Loss domain * other condition					0.17
					(0.03)**
UWD * Loss domain * other cond.					-0.07
					(0.06)
Constant	0.70	0.53	0.70	0.56	0.70
	(0.03)**	(0.04)**	(0.04)**	(0.03)**	(0.03)**
Observations	2485	2488	2489	2484	4973

The bar graph below (Figure 7) shows the mean correct choices made by each group in their respective domains and conditions. Comparing the slopes between the bars of this graph with the results from the GLS model results below, gives a good indication of the extent of differences between the results of UWD participants and controls.

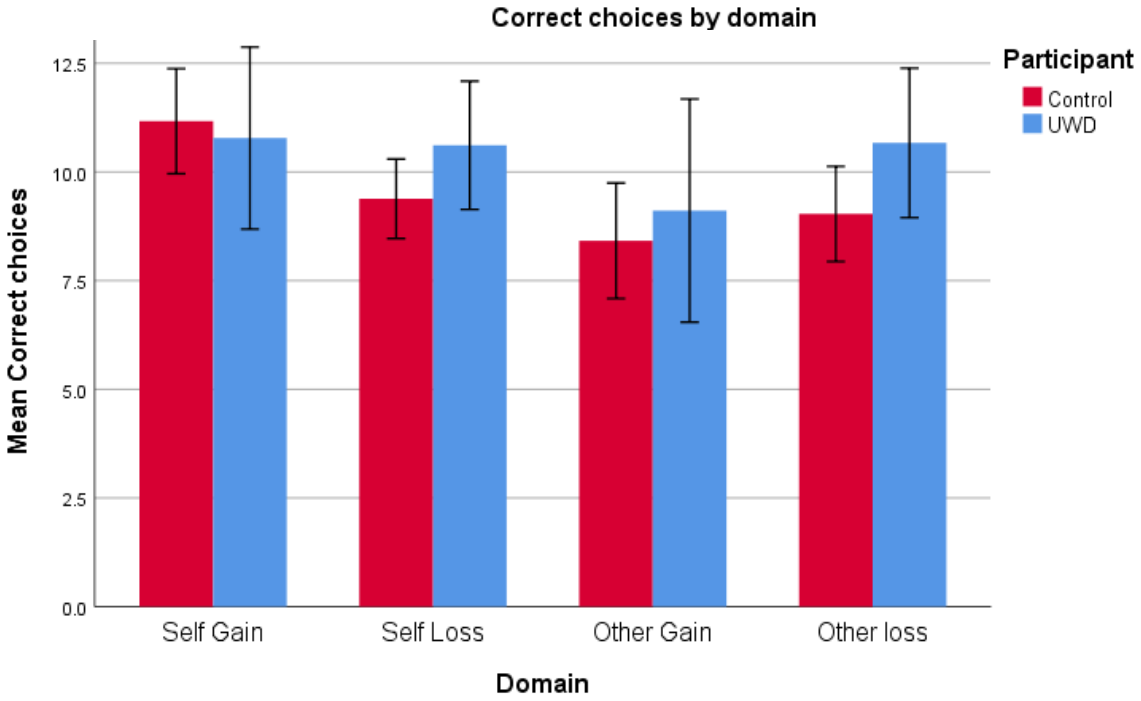

Figure 7:Bar graph representing mean number of correct choices made by participants across domains and conditions. Error bars indicate 95% confidence interval.

Table 4: Summarised mean correct choices and standard deviations for UWD and controls within each dissected domain and condition.

	Self		Other		Gain		Loss	
	Average correct	**SD**	**Average correct**	**SD**	**Average correct**	**SD**	**Average correct**	**SD**
Control	64.22	7.12	54.53	3.85	61.20	5.16	57.55	5.93
UWD	66.84	6.01	61.81	6.70	62.15	4.90	66.49	8.30

Table 5: Summarised mean correct choices and standard deviations for UWD and controls within each domain and condition as conducted during the reinforcement learning paradigm.

	Self Gain		Self Loss		Other Gain		Other Loss	
	Average correct	**SD**	**Average correct**	**SD**	**Average correct**	**SD**	**Average correct**	**SD**
Control	69.79	7.81	58.65	8.48	52.60	5.07	56.46	3.90
UWD	67.36	5.85	66.32	9.91	56.94	6.66	66.67	12.11

4.1 In the self-condition:

As was found with a GLS- random effects model, the control participants were 13 percentage points ($p < 0.01$) less likely to choose the correct symbol in the Loss domain compared to the Gain domain. The UWD participants, however, did not make fewer correct decisions in the Loss domain compared to the Gain domain, which is significantly different from the reduction in correct decisions from gains to losses observed in the control participants. The interaction effect shows that the difference between the correct decisions in the Gain and Loss domain was 13 percentage points ($p < 0.01$) smaller among the UWD participants compared to the control participants.

4.2 In the other-condition:

We observe from the GLS-random effects model that control participants chose the correct symbol for others 4 percentage points more often in the Loss domain compared to the Gain domain. This difference is only marginally significant ($p < 0.10$). Again, the UWD participants made more correct decisions than the control participants in the Loss domain. The increase from the Gain to the Loss domain is 5 percentage points more among UWD participants compared to control participants. This difference is however not significant ($p = 0.25$). Visual inspection of the lower right line graph in figure 11 shows the noticeable spike in correct choices of UWD participants between trials 5 and 12, which stands in contrast to the relatively consistent performance of controls. The line graphs in

figure 10 and figure 11 indicate a marked variance in the pattern of performance across trials for UWD participants in Other Loss domain when comparing to the same groups' performance in the Other Gain domain. This stands in contrast to the performance of controls between Other Loss and Other Gain, which seems to show little variance across trials in either domain.

4.3 In the Gain domain:

The GLS-random effects model indicates that control participants chose the correct symbol 17 percentage points ($p < 0.01$) less often in the other-condition compared to the self-condition. The UWD participants also chose the correct symbol less often in the other-condition compared to the self-condition, although their slope is not significantly different from the reduction among control participants ($p = 0.68$). The line graphs in Figure 9 and 10 present similar performances across trials, with both UWD's and controls showing a possible steady learning rate from trial 1 to 16, as well as both showing increased correct choices in the Self condition from the Other condition.

4.4 In the Loss domain:

Finally, when looking at the Loss domain only, both UWD and control participants had strikingly similar results between their respective conditions (Self and Other). Both groups chose the correct symbol similarly often in each condition (for themselves and for someone else). There was thus no difference in correct decisions between Self and Other conditions for UWD and control participants ($p > 0.13$). These results from the GLS model echo in the visual inspection of the line graphs in Figure 8 and Figure 11. An interesting observation is that when correct choices for all losses are pooled across conditions, UWD generally made more correct choices than control participants (10 percentage points more). This difference however, although noteworthy, was not statistically significant.

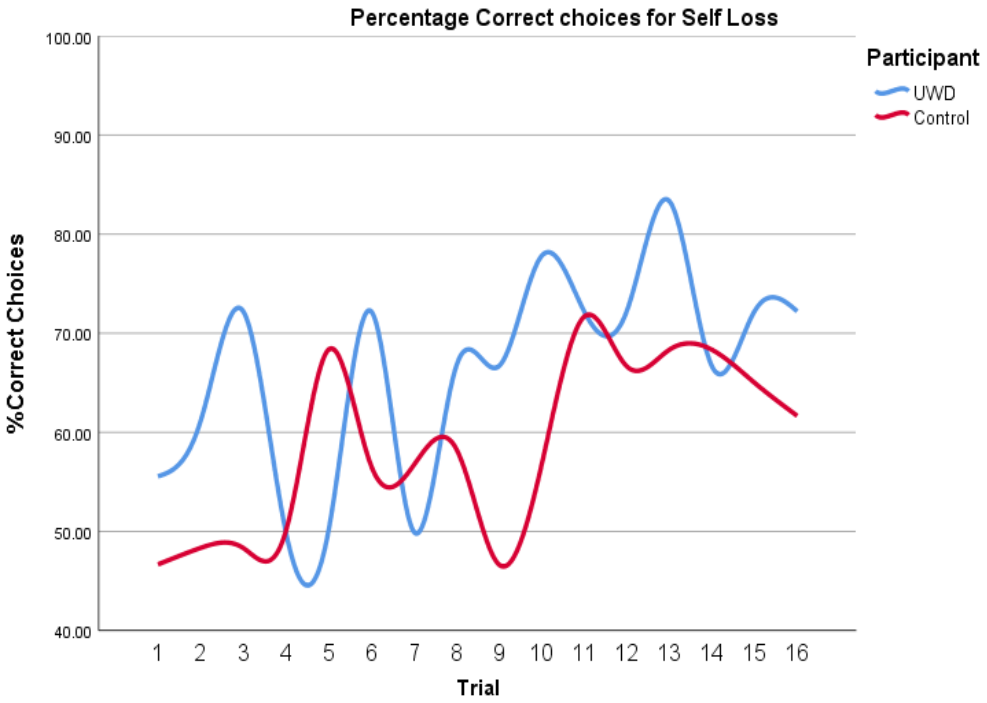

Figure 8: Line graphs for the Self Loss domain indicating the percentage of correct choices made by respective participant groups across 16 trials.

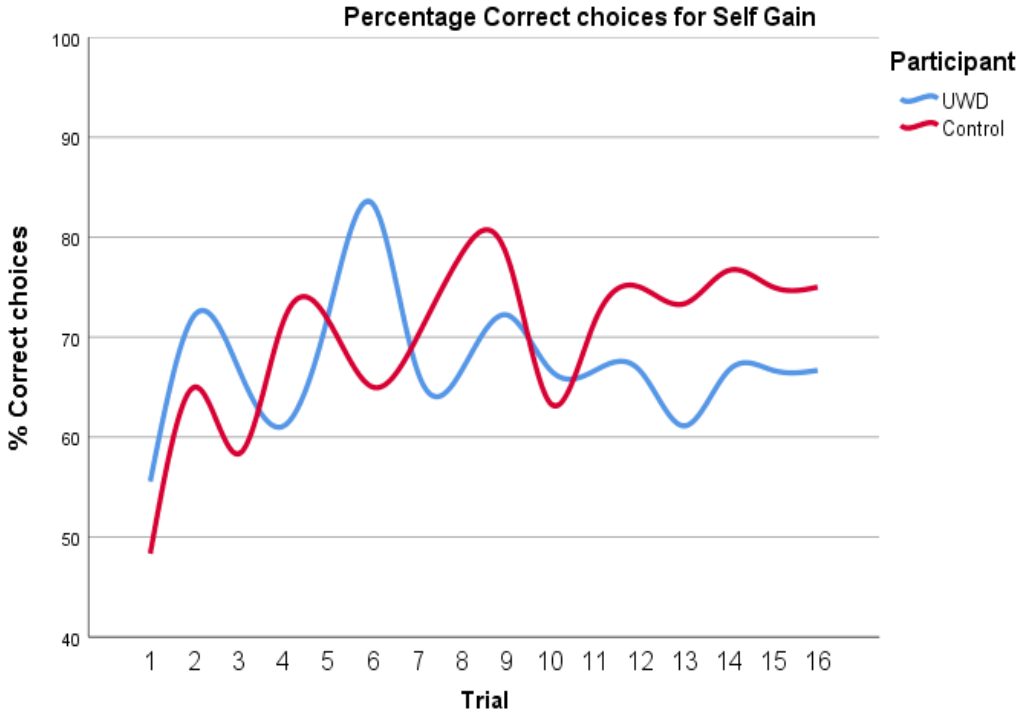

Figure 9: Line graphs for the Self Gain domain indicating the percentage of correct choices made by respective participant groups across 16 trials.

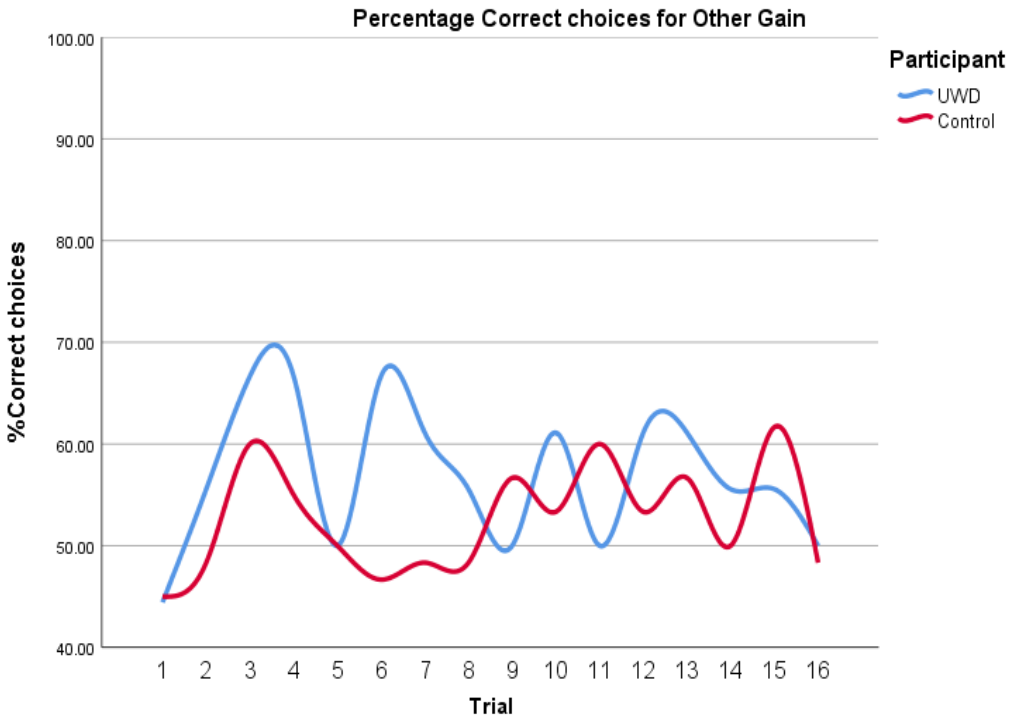

Figure 10: Line graphs for the Other Gain domain indicating the percentage of correct choices made by respective participant groups across 16 trials.

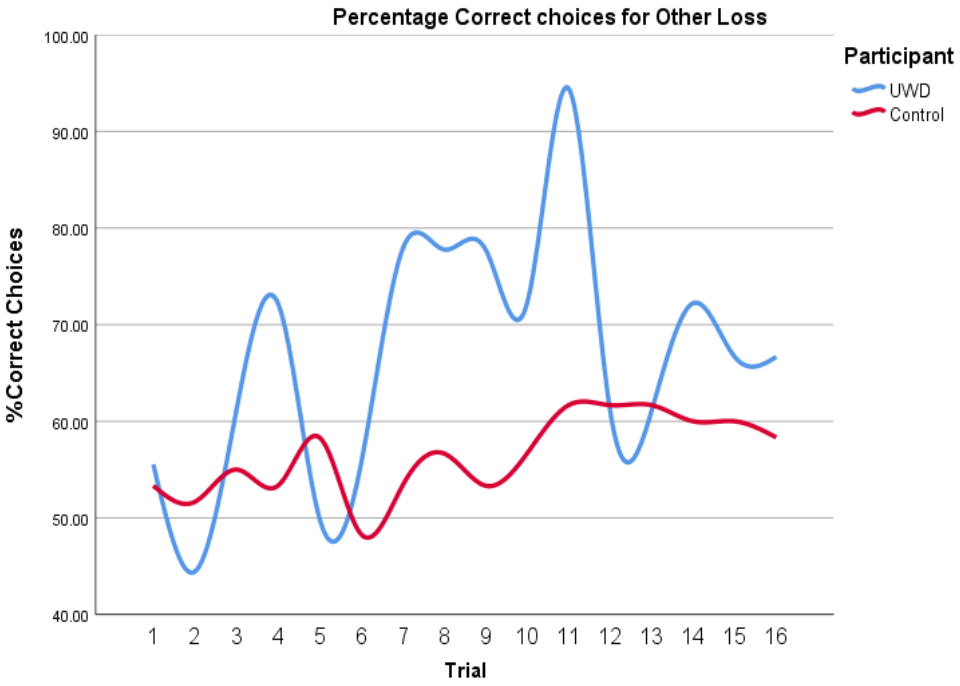

Figure 11: Line graphs for the Other Loss domain indicating the percentage of correct choices made by respective participant groups across 16 trials.

4.5 Summary of results:

When making choices for themselves, UWD participants showed no significant difference in correct choices made between Gain and Loss domains. This lack of discrimination in UWD's between gains and losses is significantly different from the results of controls, who made significantly more correct choices for themselves in the Gain domain compared to the Loss domain.

When making choices for Others, UWD participants did not make significantly more correct choices than controls, with a performance pattern that did not differ significantly from controls.

There was a trend for both controls and UWD participants to make more correct choices in the Loss domain for Others than the Gain domain, but this did not reach significance.

Both UWD participants and controls made similarly more correct decisions for themselves in the Gain domain compared to decisions made for others in the Gain domain. This difference between Self and Other was significant for controls, but not for UWD participants.

No group differences were found in the Loss domain between choosing for themselves or for others. UWD participants did however show a trend towards making more correct choices in general when choosing to avoid losses than controls, although this did not reach statistical significance.

5. Discussion

I studied the effect of BLA lesions, on social and economic decision-making, an important aspect of human cognition in an ever-changing social and economic environment. Although rodent and mammal studies have investigated the role of the BLA in decision-making as an integrative and evaluative neural structure (Balleine, Killcross, & Dickinson, 2003) (Jovanovic & Ressler, 2010), the translation of these findings to humans remains deficient.

Research in humans typically investigates themes of emotion, learning and memory using the amygdala as a homogenous structure. The unique roles of the subnuclei, not to mention their antagonistic properties, however demand individual attention for the successful translation of mammal research to humans.

5.1 Economic decision-making

Control participants made significantly fewer correct decisions for themselves in the Loss domain, compared to the Gain domain, whereas UWD participants did not differ in their choices between gains and losses, a significantly different result than that of controls. To interpret these results, it is important to view economic gains as a positive feedback from a correct choice. The possible outcomes in the Gain domain were either an increase in monetary winnings, or for the monetary winnings already accumulated to remain unchanged. In other words: either win something or win nothing. The economic losses, however, can be regarded as negative feedback from an incorrect choice. The possible outcomes in the Loss domain were either a decrease of monetary winnings already accumulated, or no losses. In other words: either lose something or no loss occurs. Making a correct decision in the Loss domain could therefore be an indicator of loss aversion, since the participant made a correct choice that resulted in the avoidance of a loss.

With this clarification in mind, we can then make either one of the following arguments from the first result: 1. UWD participants were unable to discriminate between whether an economic outcome would be beneficial or disadvantageous. 2. UWD participants showed improved decision-making during loss-aversion, however their performance in Gain-related decisions did not differ from controls.

The first argument, which states that BLA lesions could decrease the ability to predict the valence of an outcome, might be supported by earlier research outlining the role of the BLA as a salience detector and cue processor (Kapp, Whalen, Supple, & Pascoe, 1992) (Esber & Holland, 2014). Rodent research has found that BLA lesions cause indifference to the likelihood of an outcome being

either costly or beneficial, as rats were unable to discriminate between rewarded and unrewarded actions (Ghods-Sharifi, St.Onge, & Floresco, 2009). Similar rodent studies had comparable results (Balleine, Killcross, & Dickinson, 2003) (Saddoris, Gallagher, & Schoenbaum, 2005), attributing their findings to the critical role of the BLA in the integration of prediction cues and outcomes to guide behaviour (Ghashghaei & Barbas, 2002) (Gallagher & Schoenbaum, 1999) (Shi & Cassell, 1998).

The BLA has been found to encode both aversive and rewarding outcomes during reinforcement learning (Baxter & Murray, 2002), which could possibly explain the lack of discrimination between results in the Gain and Loss domains seen in UWD for themselves. Previous work on this same group of UWD participants found that they had decreased abilities to learn probabilities between stimuli and their predictive ques during fear-conditioned learning (Klumpers, Morgan, Terburg, Stein, & van Honk, Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage, 2015). Strong bidirectional connections exist between the BLA and the orbitofrontal cortex (OFC), which form a crucial circuit for acquiring and utilising associations in learning (Saddoris, Gallagher, & Schoenbaum, 2005). This has been evident in individuals with either OFC or BLA lesions whom display impairment in identifying and utilising the motivational significance of cues to guide actions in the Iowa gambling task (Bechara A. , Damasio, Damasio, & Lee, 1999).

The significantly different findings between Self-Gains and -Losses for controls and UWD could also be a product of the dissociable systems responsible for predictions between Gain- and Loss-related values (Tremblay, et al., 2014). It has already become evident that the ventral striatum could be responsible for expressing only Gain-related predictions and associated prediction errors. This was seen in both rodent (Tremblay, et al., 2014) and human (Yacubian, et al., 2006) research in patients with Parkinson's' disease. The ventral striatum, of which the nucleus accumbens is the major component, receives vital input from the BLA (Hauber & Sommer, 2009). This input from the BLA, in the form of value-generated representations, is projected to the components of the reward system

(Cardinal & Howes, 2005), the mesolimbic dopaminergic system (St Onge & Floresco, 2009) and frontal lobe regions (Floresco & Tse, 2007), and contributes to the encoding of Gain-related values. The absence of BLA- generated input to the ventral striatum could thus present in the UWD participants as a decreased drive to seek awards when compared to avoiding losses. This statement can only be true if UWD results were consistently better in all domains and conditions, indicating a higher baseline performance than controls. A higher overall baseline performance would then suggest a deficit in discrimination between values of anticipated economic outcomes, an interpretation for which there is insufficient evidence at this stage.

However, when considering the second argument for the results of the first finding, the performance of the UWD participants can be viewed as enhanced abilities in Loss-related decision-making, rather than deficits in Gains. Viewed from this perspective, I suggest that BLA lesions did not affect Gain-related decision-making, but resulted in improved loss-aversion when compared to controls.

Rodent research has found that BLA lesions result in hypersensitivity to the costs in decision-making tasks (Ghods-Sharifi, St.Onge, & Floresco, 2009). Applying this to humans could present as a heightened awareness of potential losses, where greater effort is applied to avoid costs. Therefore, a potential loss would be a greater cost (worst outcome in the Loss domain) than a potential stagnation of earnings (worst outcome in Gain domain), requiring more effort to circumvent. This could be a possible explanation of the findings here.

A different rodent study saw an increase in the amount of correct responses in a choice task following negative feedback in BLA lesioned rats (Izquierdo, et al., 2013). After committing an error in a decision-making task, BLA lesioned rats displayed enhanced performance and adaptive choice behaviours. The mechanism prescribed implicates the reward-prediction circuit between the OFC, inferotemporal cortex and the rhinal cortex, which is vital for the processing of sensory attributes of reward (Izquierdo & Murray, 2007) (Rudebeck & Murray, 2008). As was also confirmed in the working memory research conducted by Morgan et al., the BLA and OFC function as a competitive

network and lesions to the BLA would result in reduced attentional bias (Morgan, Terburg, Thornton, Stein, & van Honk, 2012). During the Loss domain, participants were only faced with either negative feedback or neutral feedback. If the rodent research can be translated to humans, it could indicate a similar response in the UWD participants whereby their performance in the Loss domain was improved due to the presence of negative feedback.

Another mechanism that could be at play in the BLA lesioned participants, is that of a hypervigilance for fear. Previous research on this same UWD group of participants found that BLA lesions result in a hypervigilance for innate unconditioned fear (Terburg, et al., 2012). This overreaction to fear is also found in non-human mammal models of BLA lesions (Macedo, Cuadra, Molina, & Brandão, 2005) (Martinez, de Oliveira, & Brandão, 2007) (Tye, et al., 2011). The proposed mechanism of action by Terburg et al. is the over-resourced action of the CMA without the inhibition of the BLA to innate danger cues. The CMA can be considered as the centre of behavioural output in the amygdala, with its projections to areas of the brain that regulate emotion, such as the brain stem and hypothalamus (Heimer, Harlan, Alheid, Garcia, & De Olmos, 1997). The BLA can, either via direct or indirect (via the PFC) connections with the CMA, inhibit or promote behavioural output (Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003) (Garcia, Vouimba, Baudry, & Thompson, 1999).

The finding that UWD participants had increased economic loss-aversion stands in contrast to similar studies on UWD (De Martino, Camerer, & Adolphs, 2010). This is likely because these experiments were conducted on humans with complete amygdala damage, sometimes even expanding into contiguous structures (Adolphs R. , Tranel, Damasio, & Damasio, 1994) (Hurlemann, et al., 2010) (Siebert, Markowitsch, & Bartel, 2013).

It was found that BLA damage led to a lack of the valence of outcomes between gains and losses in economic decision-making. Taken together, the findings here on economic decision-making therefore point to the important role of the BLA as a salience detector, with lesions to this region resulting in reduced bias to the valence of potential economic outcomes, regardless of whether

these concern costs or benefits. The findings may however also indicate that lesions of the BLA can produce loss-aversion due to hypervigilance for fear and the lack of inhibition of the CMA by the BLA.

5.2 Social decision-making

When making decisions on behalf of others, both controls and UWD participants had similar patterns of choice: a trend showing more correct choices made in the Loss domain than the Gain domain. For both losses and gains, there was no difference between correct choices made by controls and UWD participants.

Research into prosocial behaviour using economic tasks, charity donation tasks and moral judgements has identified increased activity in the dorsolateral prefrontal cortex, ventral striatum and anterior cingulate cortex (Lee & Seo, 2016; Rilling & Sanfey, 2011; Moll & Schulkin, 2009; Ruff & Fehr, 2014), areas of the brain that all share strong connections to the BLA. A recent study on the neurocomputational mechanisms of prosocial learning found that reinforcement learning in the subgenual anterior cingulate cortex (sgACC) underpinned the ability of humans to learn to benefit others (Lockwood, Apps, Valton, Viding, & Roiser, 2016). Using the same experimental procedures as this study on UWD, Lockwood and colleagues found that the performance of participants in the social decision-making task was significantly increased in individuals with higher trait empathy. This was also correlated with even stronger sgACC activation (Lockwood, Apps, Valton, Viding, & Roiser, 2016). It is possible that there is increased activation of the sgACC in UWD participants, given additional resources freed up by the absence of the BLA. One can also hypothesize that BLA lesioned individuals made more correct choices during social decision-making due to their altruistic and possibly increased empathic traits, as found in previous studies on this population (Rosenberger, et al., 2019; Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013). This could indicate why the

UWD participants had a slight trend towards more beneficial choices than controls when making decisions on behalf of others, which is in line with the findings from Lockwood et al.

In a rodent study on the effect of BLA lesions in a Prosocial Choice Task, researchers found that rats with excitotoxic lesions of the BLA were significantly less likely to choose a mutual reward for themselves and a partner rat, than only for themselves (Hernandez-Lallement, van Wingerden, Schäble, & Kalenscher, 2016). However, when making self-orientated choices about rewards, the lesioned rats showed no difference in choice from sham-operated rats. The study therefore concluded that the BLA plays a vital role in social decision-making, but not in the performance of non-social reward choices. Another study, this time on non-human primates, found the BLA to play the central role in prosocial rewards for others (Chang, et al., 2015). This statement seems to contradict previous findings on BLA-damaged individuals (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013), who made generous economic investments to strangers during a one-shot trust game. Comparing results from a trust game and that of economic decision-making on behalf of strangers seems unfounded at first, given that the trust game aims to investigate the ability of individuals to adjust their behavioural output towards others based on the behavioural feedback received from them. It is however important to note that a number of similar features exist across these paradigms.

Humans are rational and self-driven in their economic decisions, according to classical economic models (Hollis & Nell, 1975). On the other hand, contemporary models suggest that, not only are economic decisions instrumental, but they can be impulsive and emotionally driven too (Fehr & Camerer, 2007). This is especially relevant in social economic decisions, which usually occur after feedback from a trustee is received. Humans have an inborn inclination to altruism, as observed in young children (Eisenberg N. , 1992; Eisenberg, Fabes, & Spinrad, 2006), that seems to decline with age and life-related experience. The fading of altruism can possibly be attributed to updates of social experiences, where altruistic behaviour is not reciprocated. This ability to update behaviour and

learn from social experiences is dependent on the BLA (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013; Eisenberg, Fabes, & Spinrad, 2006; Rand, Greene, & Nowak, 2012).

The finding by Van Honk and colleagues that bilateral BLA damage is associated with increased prosocial behaviour during a trust game has been attributed to parallel processing between the subregions of the amygdala (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013). Thus, the BLA is involved in instrumental choice behaviours and the CMA in affective-impulsive behaviours. The absence of a functional BLA impairs rational, self-directed choice behaviours by diminishing both direct and indirect pathways of inhibition regulation. This allows for over-resourced actions by the CMA, which results in increased altruistic economic behaviour. The current findings in this thesis do not necessarily reflect this; however, it is important to note that economic decisions on behalf of strangers involve a completely different neural mechanism than economic investments in strangers with the prospect of returns. During the latter paradigm, continuous updating of behaviour is required based on the feedback received from trustees. A recent study on this same group of participants (Rosenberger, et al., 2019), found that lesions to the human BLA attenuated social experiential learning. In this experiment, the same group of participants were unable to update their behaviour towards selfish trustees.

Contrary to the findings from the abovementioned research (Van Honk, Eisenegger, Terburg, Stein, & Morgan, 2013), the UWD participants in this study did not necessarily make more "generous" choices for others in the Gain domain. The nature of these gains for others is not entirely explicit. The decisions in this paradigm involved learning which outcome from two different visual stimuli would be most beneficial: a more unconscious approach to social decision-making. A completely different outcome might be expected if these individuals were to perform a task where explicit gains or donations are made to others. This would be more in line with the findings on social neuroeconomics of the previous studies on this population group. The UWD participants in the current study were still not maleficent towards others though, since they put a great amount of

effort into avoiding losses to others. In fact, there was hardly any difference between the amount of correct choices to avoid a loss between Self and Others for UWD, a strikingly different result from that of controls.

A possible future paradigm to look into is the implementation of explicit visual stimuli in the form of an image of the trustee during this task. This visual feedback, in the form of human faces, might result in different findings than that of the current study. Stock images of actors are usually utilised in similar tasks, however participants are made to believe that they are indeed interacting with these specific individuals in real-time, albeit anonymously. The role of visual feedback from faces cannot be underestimated in decision-making tasks. The BLA has been found to have strong projections to the primary visual cortex in cats (Chen, Zhu, & Shou, 2009). Presenting images of participating players (or actors) could contribute to the emotional valence of the social decision-making experience, possibly resulting in findings that could reflect previous outcomes of research on social behaviour in BLA lesioned humans.

The BLA damaged individuals in this study did not make more prosocial correct decisions for others than for themselves, which partially supports the findings in the BLA-lesioned rat and primate studies (Chang, et al., 2015; Hernandez-Lallement, van Wingerden, Schäble, & Kalenscher, 2016) and also in humans (Lockwood, Apps, Valton, Viding, & Roiser, 2016).

Taken together, the data here indicate that UWD participants made more correct choices than controls (with the marginal exception of Self Gains) in the decision-making task, that is, more correct choices than controls in order to achieve the best possible outcome in each domain for themselves and others. If this is proven true in future studies, this may be a product of paradoxical facilitation of working memory (Morgan, Terburg, Thornton, Stein, & van Honk, 2012) after BLA lesions, an attribute that might enhance performance in a reinforcement learning task (Collins & Frank, 2012).

6. Limitations and directions for future research:

Several limitations deserve emphasis. First, there was a lack of visual representation of strangers during the social decision-making paradigm. Increasing the valence of social stimuli could result in more reliable results as the participant would constantly be reminded of the trustee. Future research could include this to evaluate whether social feedback in the form of visual representation of others influences the performance of BLA lesioned individuals.

Second, habitual responses to certain paradigms may have occurred. The participants in the Namaqualand cohort have been exposed to these and similar research paradigms in the past. Although extended periods of time preceded data collection which expanded over many years, memory of previous studies could influence the participants' experience of especially social paradigms. Researchers always aim to create realistic scenarios surrounding the whereabouts of "anonymous trustees or players", however the possibility does exist that participants could have formed their own ideas around the truthfulness of scenarios in social experiments. In future studies, a carefully curated debriefing could be implemented to avoid losing the trust of participants, while at the same time ensuring believability of scenarios.

Third, although the participants in this study have been involved in research for many years, their exposure to technological paradigms and apparatus are extremely limited. One can safely assume that, for most participants, the only experience with technological methods such as typing on the keyboard of laptops or using a touchscreen have been during contact sessions with this research group. This only occurs once in about two years, which could add to intimidation by these processes. I have tried to minimise such intimidation by over-simplifying technological interaction, such as only requiring one or two keys to press during interactions and labelling these keys with contrasted colour stickers. The possibility that technology, even when simplified, could overwhelm these under-exposed individuals, cannot be discarded.

Fourth, this study did not consider the learning rate during decision-making paradigms. After the recent publication of another study on this group (Rosenberger, et al., 2019), one can expect to find valuable information about the rate of learning which symbols are associated with gains or losses during a reinforcement learning task, as this involves continuous value-updating of symbols. The ability or inability of the BLA to adapt the choices made after experiential feedback could provide us with a better understanding of these results in decision-making. Reinforcement learning and learning rate is central to adaptive decision-making and a next venture should consider this.

7. Conclusion

This study aimed to identify a possible role of the human BLA in social and economic decision-making. The findings show that UWD participants were not impaired in either social or economic decision-making. Control participants seem to show a performance preference for specific outcomes of their choices, but UWD participants lacked this same discrimination between the valence of outcomes across domains. It appears that the human BLA is not required to learn general associations of stimulus-responses that are not emotionally or valuably charged. A preliminary trend indicates that the decision-making performance of BLA lesioned individuals shows less variance than controls, a possible product of enhanced working memory. This should however be validated in future research.

BLA damaged individuals showed no difference in social decision-making performance from controls. Based on these results, one could however predict a possible trend that favours others during social decision-making in UWD participants. Better performance in social decision-making by UWD participants could be due to their increased altruism and empathy. One can hypothesize that future inclusion of facial feedback from trustees could provide more definitive results.

Taken together, these findings demonstrate further roles of the human BLA in prosocial behaviour, providing a unique translation from animal findings to humans. The data builds on previous work on both mammalian studies and the current cohort of UWD individuals.

This thesis presents the novel finding that humans with BLA damage show reduced bias to the valence of potential economic outcomes, regardless of whether these pertain to costs or benefits. Applying this information to a conceptual framework of abnormal decision-making in psychiatric disorders could aid in the development of targeted interventions to improve clinical outcomes of patients.

8. Appendix

8.1 Xtreg data results GLS model

```
. xtreg correctchoice uw##gainloss if selfother==1

Random-effects GLS regression                   Number of obs     =      2,488
Group variable: id                              Number of groups  =         26

R-sq:                                           Obs per group:
     within  = 0.0032                                         min =         94
     between = 0.0047                                         avg =       95.7
     overall = 0.0033                                         max =         96

                                                Wald chi2(3)      =       7.92
corr(u_i, X)   = 0 (assumed)                    Prob > chi2       =     0.0477

------------------------------------------------------------------------------
correctcho~e |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          uw |
          UW |  -.0036394   .0729276    -0.05   0.960    -.1465748     .139296
             |
    gainloss |
        loss |   .0370359   .0219009     1.69   0.091     -.005889    .0799608
             |
 uw#gainloss |
    UW#loss  |   .0521043   .0456374     1.14   0.254    -.0373434    .1415519
             |
       _cons |   .5279449   .0350443    15.07   0.000     .4592593    .5966306
```

```
-------------+----------------------------------------------------------------
     sigma_u |  .14060048
     sigma_e |  .47932201
         rho |   .0792267   (fraction of variance due to u_i)
------------------------------------------------------------------------------

. est store m1

. xtreg correctchoice uw##gainloss if selfother==0

Random-effects GLS regression                   Number of obs     =      2,485
Group variable: id                              Number of groups  =         26

R-sq:                                           Obs per group:
     within  = 0.0161                                         min =         94
     between = 0.0156                                         avg =       95.6
     overall = 0.0161                                         max =         96

                                                Wald chi2(3)      =      40.59
corr(u_i, X)   = 0 (assumed)                    Prob > chi2       =     0.0000

------------------------------------------------------------------------------
correctcho~e |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          uw |
          UW |  -.0220552   .0719246    -0.31   0.759    -.1630248    .1189143
             |
    gainloss |
        loss |  -.1324586   .0208908    -6.34   0.000    -.1734037   -.0915134
             |
 uw#gainloss |
    UW#loss  |   .1263352   .0434672     2.91   0.004     .0411411    .2115293
```

```
             |
       _cons |   .6956663   .0345591    20.13   0.000     .6279318    .7634009
-------------+----------------------------------------------------------------
     sigma_u |  .13971772
     sigma_e |  .45651588
         rho |  .08564573   (fraction of variance due to u_i)
------------------------------------------------------------------------------

. est store m2

. xtreg correctchoice uw##selfother if gainloss==0

Random-effects GLS regression                   Number of obs     =      2,489
Group variable: id                              Number of groups  =         26

R-sq:                                           Obs per group:
     within  = 0.0315                                         min =         94
     between = 0.0024                                         avg =       95.7
     overall = 0.0282                                         max =         96

                                                Wald chi2(3)      =      80.05
corr(u_i, X)   = 0 (assumed)                    Prob > chi2       =     0.0000

------------------------------------------------------------------------------
correctcho~e |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          uw |
          UW |  -.0218399   .0812536    -0.27   0.788     -.181094    .1374143
             |
   selfother |
        self |  -.1672816    .020822    -8.03   0.000     -.208092   -.1264711
             |
uw#selfother |
```

```
    UW#self  |    .017976   .0432833     0.42   0.678    -.0668577    .1028097
             |
       _cons |    .695451   .0390397    17.81   0.000     .6189346    .7719674
-------------+----------------------------------------------------------------
     sigma_u |  .16169793
     sigma_e |  .45532878
         rho |  .11198939   (fraction of variance due to u_i)
------------------------------------------------------------------------------
est store m3

. xtreg correctchoice uw##selfother if gainloss==1

Random-effects GLS regression                   Number of obs     =      2,484
Group variable: id                              Number of groups  =         26

R-sq:                                           Obs per group:
     within  = 0.0008                                         min =         93
     between = 0.0554                                         avg =       95.5
     overall = 0.0050                                         max =         96

                                                Wald chi2(3)      =       3.17
corr(u_i, X)   = 0 (assumed)                    Prob > chi2       =     0.3660

------------------------------------------------------------------------------
correctcho~e |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          uw |
          UW |   .1046536   .0703352     1.49   0.137    -.0332008    .2425079
             |
   selfother |
        self |   .0023356   .0217779     0.11   0.915    -.0403483    .0450194
```

```
              |
  uw#selfother |
      UW#self  |  -.0563862   .0454226    -1.24   0.214    -.1454128    .0326404
               |
         _cons |   .5628221   .0337861    16.66   0.000     .4966026    .6290416
  -------------+----------------------------------------------------------------
       sigma_u |  .13448403
       sigma_e |  .47640193
           rho |  .07380674   (fraction of variance due to u_i)
  ------------------------------------------------------------------------------
  est store m4
```

```
. xtreg correctchoice uw##gainloss##selfother

Random-effects GLS regression                   Number of obs     =      4,973
Group variable: id                              Number of groups  =         26

R-sq:                                           Obs per group:
     within  = 0.0175                                         min =        188
     between = 0.0129                                         avg =      191.3
     overall = 0.0173                                         max =        192

                                                Wald chi2(7)      =      88.53
corr(u_i, X)   = 0 (assumed)                    Prob > chi2       =     0.0000

------------------------------------------------------------------------------
---
        correctchoice |      Coef.   Std. Err.      z    P>|z|     [95% Conf.
Interval]
```

```
---------------------+------------------------------------------------------------
---
                  uw |
                  UW |   -.022089     .06815    -0.32   0.746    -.1556607
.1114826
                     |
             gainloss |
                loss |  -.1328718   .0216338    -6.14   0.000    -.1752732   -
.0904703
                     |
          uw#gainloss |
             UW#loss |   .1267337   .0450133     2.82   0.005     .0385093
.2149581
                     |
            selfother |
                self |  -.1674387   .0216224    -7.74   0.000    -.2098179   -
.1250596
                     |
         uw#selfother |
             UW#self |   .0181332   .0449473     0.40   0.687    -.0699619
.1062282
                     |
   gainloss#selfother |
           loss#self |   .1698048   .0305787     5.55   0.000     .1098716
.229738
                     |
uw#gainloss#selfother |
        UW#loss#self |  -.0746632    .063672    -1.17   0.241    -.1994581
.0501317
                     |
```

```
               _cons |   .6957001   .0327468    21.24   0.000     .6315175
.7598828
----------------------+------------------------------------------------------------
-
             sigma_u |  .12955612
             sigma_e |  .47300443
                 rho |    .069786   (fraction of variance due to u_i)
------------------------------------------------------------------------------
-


. est store m5
```

8.2 Probabilistic reinforcement task instructions:

Developed using Ztree version 3.6.7 software.

Participants will perform a probabilistic reinforcement learning task where they are required make decisions based on the learned probability that one of two symbols could be result in monetary reward or loss. These two symbol pairs are represented by Chinese symbols with distinct individual features. One pair is associated with monetary gains (a probability of 75% to win 1 point or a probability of 25% to win nothing), and a second pair is associated with a loss (a probability of 75% to lose 1 point or a probability of 25% to lose nothing). Participants will perform this task in two different learning contexts: self and prosocial. Participants will be instructed that when they are playing for themselves they will receive any money won. When they are playing for the other person, that participant will receive the money. The "other participant" is in fact fictitious and no real participants are involved. Participants will be informed that the other participant is not aware that they are performing a task where they could earn extra money and that any money they win will be given to the other participant anonymously.

Self-blocks begin with the instruction "play for yourself" and will have the word "you" written above all choice symbols and outcomes. Prosocial blocks begin with the instruction "Play for the other person" and will have the words "other person" written above all choice symbols and outcomes. This ensures that participants are explicitly aware whether they are making decisions for themselves or for the other participant. Participants will first practice one block of the task in a separate session after the scanning session to familiarize themselves with the experimental task. During this practice they will be instructed that the outcomes of the practise rounds will not be converted into any payment.

Procedure.

The procedure will be explained to the participants by the investigating student. First, a quick verbal overview will be given by the instructor, explaining the background, methods and aim of each experiment. With each sitting in front of their respective screens, they will then read the instructions along with the facilitator as it appears on the screen. Following this, all participants will simultaneously watch a simulated play-through of the procedure on their respective computer screens. Any questions will be answered hereafter. Participants will be asked to fill in control questions that test whether they comprehend the task, before an interactive practice run is done by each participant on their own screen. After the instructor is satisfied with the performance in the practice round of each participant, they will commence the task.

On the first screen, the phrase “play for yourself” or “play for someone else” will appear. The participants will then see two symbols on their screen, of which they must choose any one they prefer. After a few trials, participants should begin to know which pair of symbols is associated with gains and which with losses, and be able to predict the outcome of a specific symbol with reasonable success.

As the participants take part in this game, they will earn points during each session. These points are accumulative which means that gains will result in more points and losses will result in a decrease of accumulated earnings. The total earnings from this task is automatically calculated by the software and the amount is paid out to them in cash at the end of all the tasks. Throughout the entire process, the instructor will be in the same room as the participants should they require assistance, however out of sight so that they do not feel as if they are being watched. Participants are always consulted on their level of comfort and, should any one of them feel intimidated by the presence of the instructor, they will be moved to a more private spot within the same lab.

Trial structure:

Each block will begin with with an instruction screen that indicates who would receive the outcomes (Self or Other participant) for 2 seconds. This will be followed by the presentation of two abstract stimuli for 3 seconds during which participants are required to select one of. These stimuli are plain Chinese symbols in black font. If no response is indicated during this time, the words “too late” will appear in red on the screen. The selected option will be shown for 300 ms, followed by a delay (2,5 seconds), then by the outcome of their choice (+R3/ nothing /-R3). The side of the screen on which the two symbols are presented will be counterbalanced so that participants cannot perform action-based learning. They will also be instructed that the side of the stimulus does not matter, to encourage them not to learn based upon the action they had performed but to learn the contingencies between the stimuli regardless of position and outcome.

Each participant will do 192 trials in total, 48 Self Gain, 48 Self Loss, 48 Other Gain, and 48 Other Loss, presented in 12 blocks of 16 trials. Blocks will be presented in pseudorandom order, with the same block type never presented twice in a row.

Participant instructions:

“In this experiment you will see a pair of symbols on each trial and you need to select one of them.

“You will receive money for some of your choices and you might lose money for others, of which the total amount will be paid out to you at the end of the experiment, so the more correct choices you make, the more extra money you will earn. The two symbols in each pair are not the same in terms of how often they give you money: some of the symbols will give you money more often than others. Within each pair, both symbols have their own meaning, regardless of where it appears on the screen (so left and right are not important) or when it occurs in the task, but in each pair, the potential to either win or lose money will be constant for that specific pair. You will therefore soon begin to notice which pair is the “winning pair” and which is the “losing pair”.

“You will play the task in two conditions, for yourself and for the other participant. When you are playing for yourself, you will receive any money you win. When you are playing for the other participant, they will receive any money you win for them. However, the other participant won’t know how much money you earn for them until they leave the experiment and they do not know that you are performing a task where you could win extra money for them.

“Respond using the left and right arrow keys to make your selection. Try to respond as quickly as possible, you have about 2 seconds to make your choice.”

8.3 Human research ethics approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 883-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

16 March 2018

HREC REF: 740/2017

Prof J Van Honk
Psychiatry & Mental Health
J-Block, GSH

Dear Prof Van Honk

PROJECT TITLE: SOCIAL AND ECONOMIC DECISION-MAKING IN URBACH-WIETHE DISEASE (Msc Candidate - Ms J Fourie)

Thank you for submitting your response to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 March 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Jorique Fourie will also be involved in this study.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-45 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shumitte.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

08 May 2018

HREC REF: 839/2016

Prof J Van Honk
Psychiatry & Mental Health

Dear Prof Van Honk

PROJECT TITLE: THE HUMAN BASOLATERAL AMYGDALA AND SOCIAL -EMOTIONAL BEHAVIOUR: FURTHER STUDIES IN URBACH-WIETHE DISEASE

Thank you for your response to the HREC letter dated 14th February 2018 that requested clarification on issues noted in review of the annual progress report for the above study.

The annual progress report has been approved. Formal ethics approval has been renewed until 30 May 2019.

The HREC note that research ethics approval is pending from the Royal Holloway Research Ethics Committee, to support the involvement Prof Michael Naef in providing supervisory assistance to Ms Jorique Fourie. Please submit a copy of the formal research ethics approval letter from the Royal Holloway Research Ethics Committee once approval has been granted.

Please note that if there are any plans to transfer data to an international collaborator, participants must be informed and give written informed consent for data to be transferred for analysis purposes.

In addition, a material transfer agreement is required for out-going data or samples. Please contact the UCT RCIPS Office for guidance if a material transfer agreement is needed.
Once finalised, material transfer agreements must also be submitted to the HREC for approval.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

signature removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

8.4 Informed consent form (English version)

Department of Psychiatry and Mental Health

UCT dept of Psychiatry and Mental Helath, Groote Schuur Hospital (J2), Anzio road, Observatory

7925, Cape Town, South Africa

Phone: +27 21 4042174

URL: http://www.health.uct.ac.za/departments/psychiatry/about

---

INFORMED CONSENT FORM

TITLE OF RESEARCH PROJECT:

Social and economic decision-making in Urbach-Wiethe Disease

Research for degree purposes: MSc(Med) Neuroscience

PROJECT NUMBER:

.....

PRINCIPLE INVESTIGATOR:

Professor Jack van Honk

Department of Mental Health and Psychiatry

University of Cape Town

Anzio Road

Observatory, 7925

South Africa

RIN NUMBER .....

INFORMED CONSENT FORM FOR PATIENTS

Researchers: Prof. Jack van Honk

Prof. Dan Stein

Co-investigator: (Student investigator)

Jorique Fourie

INTRODUCTION

Dear Volunteer

You are invited to take part in a research study. This study will be conducted mostly by Jorique Fourie, a student of the University of Cape Town, as well as her supervisors, Professor Jack van Honk and Professor Dan Stein. This research is for degree purposes and will be used to qualify Ms Fourie with a Masters degree in Neuroscience. Kindly read through the following information carefully and do not hesitate to ask questions now or during the study. Your participation in this study is completely voluntary.

BACKGROUND AND PURPOSE OF THE STUDY

Urbach-Wiethe Disease (UWD) is a disease that is inherited from either one or both parents who might carry genes for this disease. UWD is not a disease that makes you sick, but rather a disease that could possibly give you symptoms like a hoarse voice, some scars on your skin, and minor problems with your memory, feelings (such as anxiety) or your thoughts.

UWD is extremely rare, only a few hundred cases have ever been recorded. South Africa has the largest concentration of individuals with UWD in the world. Namakwaland is very special because many people carry genes for UWD without even knowing it. This is because most Namakwalanders are somehow related and share the same genes. Because of the fact that we have the most UWD cases in the world, South African research is helping scientists and doctors to learn a lot about the disease that we did not know before.

This research is important because we can use the information from people with UWD to help others, even people who have problems like memory loss or anxiety disorders. Because UWD is not life-threatening and people with the disease are perfectly normal and healthy otherwise, we can get answers for questions about memory, emotions and behaviour that would be difficult to investigate in very sick people.

We would like to evaluate all South Africans with UWD (and controls without UWD residing in the same neighbourhoods) to take a closer look at their memory, thoughts, feelings and behaviour. Our purpose is to learn more about UWD and how we can help people with

similar symptoms. We hope that our research can help to make someones life a little bit easier.

The study will take place in the area where you live and will be conducted according to the Declaration of Helsinki and the guidelines of “Good Clinical Practice” (ICH). This study has been approved by the Human Research Ethics Committee of the University of Cape Town.

Should you be invited to take part in UWD-research, your transport, lunch and accommodation will be provided free of charge, where neccesary. If needed, arrangements can be made by us with your employer for leave from work, but we will first try to accomodate you n days when you are not at work. Research will take place in groups of about 4 or 5 people. That way we can do all our tests on one day. All the research activities are explained in this document.

Behavioural computer-based task

Most of the research will be done on computers. You will be asked to do certain behavioural tasks in the form of computer games. These are fun and you do not need to prepare for any of these tasks. Here is an idea of what you can expect:

Chinese symbol task: In this task you will be sitting in front of a computer alone. You will see two different pairs of pictures. Each pair contains two Chinese symbols. Your job is to press a key on the keyboard that represents one of the symbols. At first you can choose any symbol you like best. You will notice that each symbol is associated with a certain amount of

money. One of the pairs are associated with winning money, and the other pair is associated with losing money. In the “winning” pair, you should choose the symbol that will give you most winnings and in the “losing” pair you should choose the symbol that will give you the least losses. You will then repeatedly choose the symbol you like best, where after the computer will ask which one liked the most. You will do this tasks a few times for yourself and after that, you will have the chance to do the same task again, but this time you will be playing on behalf of someone else (the identity of this person is a secret). Everything you win in your round will be paid out to you after the task, and everything you win for the other person will be paid out to them at the end of their task.

POSSIBLE DISCOMFORT ASSOCIATED WITH THIS STUDY

Since we will be working on computers all day, you might find that your eyes become tired or that you feel the need to stand up for fresh air. We will however provide you with short breaks between each task. You will also have a longer lunch to regain your strenght.

POTENTIAL BENEFITS

This study holds no direct benefit to any participants, although you and many other UWD patients could benefit from our findings in the future. This study could assist doctors and scientists to better understand the disease and to create possible future treatments for UWD and other similar diseases.

REMUNERATION FOR PARTICIPATION IN THIS STUDY

Even though you will not be paid to take part in the study, you will not incur any personal costs since your accommodation, meals and travel costs will be covered where needed (this includes caregivers and control personnel). Should you incur any other travel costs, you will be reimbursed. A member of the research team will see to it that you are provided with all your basic needs for the duration of the study. This includes enough water, snacks and a good lunch.

During some tasks, you might have an opportunity to win a small amount of money as part of a game.

COMPENSATION FOR POSSIBLE INJURY OR LOSS

Since this study only includes behavioural research, no bodily harm is anticipated. However, in case of an emergency during the research period, call Jorique Fourie 0797217969.

This research study is covered by an insurance policy taken out by the University of Cape Town if you suffer a bodily injury because you are taking part in the study.

The insurer will pay for all reasonable medical costs required to treat your bodily injury, according to the SA Good Clinical Practice Guidelines 2006. The insurer will pay without you having to prove that the research was responsible for your bodily injury.

CONFIDENTIALITY

Your participation is regarded as strictly confidential. When you join the study you will be given a unique number called a RIN which will be used in place of your name to identify the information collected from you during the study. This form with your name and RIN number on it will be stored in a secure place. Your name and your RIN number will be used to identify your data from the tasks whenever you participate in the study but your name will be removed once all the data has been collected and the identity of each participant in each task has been checked and confirmed. Your data will then be stored on the study computers which are password protected with only your RIN number to identify it. This means that no other researchers who use the data will know who it belongs to. Only three senior researchers whose names appear at the front of this document (Prof. Jack van Honk, Prof Dan Stein and Jorique Fourie) will have access to this consent form which links your name to your RIN number. All these people are required to keep this information strictly confidential. The results from this study will be published in professional journals but your identity will not be disclosed at any point.

It is important to note that, because of possible symptoms of UWD, the rareity of the disease and the small recruitment area, participants could possibly be identifiable after publication. However, this can only link you to possible participation in the study, and no

direct results will point to one participant in person. Results are reported for the group and not for individuals.

THE RIGHT TO ASK QUESTIONS/ TO WITHDRAW FROM THE STUDY

You have every right to ask questions about any aspect of the study at any time.

Your participation in this study is completely voluntary. You have the right to withdraw from the study at any time. Should you decide to withdraw, it will have no impact on your future treatment and you will not be disadvantaged in any way. You are entitledd to a signed copy of this document.

Any research-related questions can be directed to:

Jorique Fourie 0797217969 or jorique.calitz@gmail.com

Prof Jack van Honk 0607506166 or jackvanh@gmail.com

If you have any questions about your rights or welfare as a research participant, please feel free to contact the UCT Faculty of Health Science Human Research Ethics Committee(HREC):

UCT HREC: (021)4066492

DECLARATION OF INFORMED CONSENT

Social and economic decision-making in UWD

I .....hereby agree to participate in this study.

I have read through this document and I understand that I had the opportunity to ask any questions.

Signed by participant: _____ on _____20____

Singed by witness: _____ on _____20____

RIN NUMBER .....

DECLARATION BY/ ON BEHALF OF RESEARCHER

I, _____, declare that I:

Explained the content of this document to : _____

Requested him/her to ask any questions so that all uncertainties could be clarified;

This conversation was conducted in the participants' mother tongue.

Signed at: _____ on _____ 20_____ .

RESEARCHER/REPRESENTATIVE:

References

Adolphs, R., & Tranel, D. (2003). Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologica, 41*, 1281-1289.

Adolphs, R., Gosselin, F., Buchanan, T., Tranel, D., Schyns, P., & Damasio, A. (2005). A mechanism for impaired fear recognition after amygdala damage. *Nature, 433*, 69-72.

Adolphs, R., Tranel, D., & Damasio, A. (1998). The human amygdala in social judgement. *Nature, 393*, 470-474.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. (1994). Impaired recognition of emotion infacial expressions following bilateral damage to the human amygdala. *Nature, 372*, 669-672.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N. J., & Zilles, K. (2005). Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anatomy and embryology, 210*, 343-352.

Anticevic, A., Barch, D. M., & Repovs, G. (2010). Resisting emotional interference: brain regions facilitating working memory performance during negative distraction. *Cognitive, Affective, & Behavioral Neuroscience, 10*(2), 159-173.

Appenzeller, S., Chaloult, E., & Velho, P. (2006). Amygdalae calcifications associated with disease duration in lipoid proteinosis. *Journal of Neuroimaging, 16*, 154-156.

Balleine, B. W., & Killcross, S. (2006). Parallel incentive processing: an integrated view of amygdala function. *Trends in neurosciences, 29*(5), 272-279.

Balleine, B., Killcross, A., & Dickinson, A. (2003). The Effect of lesions of the basolateral amygdala on intrumental conditioning. *Journal of Neuroscience, 23*(2), 666-675.

Barbas, H., Saha, S., Rempel-Clower, N., & Ghashghaei, T. (2003). Serial pathways from primate prefrontal cortex to autonomic areas may influence emotional expression. *BMC neuroscience, 4*(1), 25.

Baxter, M., & Murray, E. (2002). The amygdala and reward. *Nature Reviews Neuroscience, 3*, 563–572.

Bechara, A., & Damasio, A. R. (2005). The somatic marker hypothesis: A neural theory of economic decision. *Games and economic behavior, 52*(2), 336-372.

Bechara, A., Damasio, H., Damasio, A., & Lee, G. (1999). Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *Journal Of Neuroscience, 19*, 5473-5481.

Bechara, A., Damasio, H., Tranel, D., & Damasio, A. R. (1997). Deciding advantageously before knowing the advantageous strategy. *Science, 275*(5304), 1293-1295.

Bos, P. A., Brummelman, E., & Terburg, D. (2015). Cognition as the tip of the emotional iceberg: A neuro-evolutionary perspective. *Behavioral and Brain Sciences*, 38.

Botha, M., & Beighton, P. (1983). Inherited disorders in the Afrikaner population in southern Africa, part II: skeletal, dermal and hematological conditions; the Afrikaners of Gamkaskloof; Demographic considerations. *South African Medical Journal, 64*, 664-667.

Brand, M., Grabenhorst, F., Starcke, K., Vandekerckhove, M. M., & Markowitsch, H. J. (2007). Role of the amygdala in decisions under ambiguity and decisions under risk: evidence from patients with Urbach-Wiethe disease. *Neuropsychologia, 45*(6), 1305-1317.

Bush, G., Vogt, B. A., Holmes, J., Dale, A. M., Greve, D., Jenike, M. A., & Rosen, B. R. (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences*, 523-528.

Camerer, C. F. (2003). Behavioural studies of strategic thinking in games. *Trends in cognitive sciences, 7*(4), 225-231.

Camerer, C. F., Loewenstein, G., & Prelec, D. (2004). Neuroeconomics: Why economics needs brains. *Scandinavian Journal of Economics, 106*(3), 555-579.

Cardinal, R., & Howes, N. (2005). Effects of lesions of the nucleus accumbens core on choice between small certain rewards and large uncertain rewards in rats. *BMC Neuroscience, 6*(37).

Chan, I., Liu, L., Hamada, T., Sethuraman, G., & McGrath, J. A. (2007). The molecular basis of lipoid proteinosis: mutations in extracellular matrix protein 1. *Experimental dermatology, 16*(11), 881-890.

Chang, S. W., Fagan, N. A., Toda, K., Utevsky, A. V., Pearson, J. M., & Platt, M. L. (2015). Neural mechanisms of social decision-making in the primate amygdala. *Proceedings of the National Academy of Sciences of the United States of America, 112*(52), 16012–16017.

Chawla, M., & Miyapuram, K. P. (2018). Context-Sensitive Computational Mechanisms of Decision Making. *Journal of experimental neuroscience, 12*(1179069518809057). doi:10.1177/1179069518809057

Chen, Y., Zhu, B., & Shou, T. (2009). Anatomical evidence for the projections from the basal nucleus of the amygdala to the primary visual cortex in the cat. *Neuroscience Letters, 453*, 126–130.

Chesworth, R., & Corbit, L. (2017). The Contribution of the Amygdala to Reward-Related Learning and Extinction. In *The Amygdala: Where Emotions Shape Perception, Learning and Memories* (pp. 305-325). Sydney.

Claeys, K., Claes, L., & Van Goethem, J. (2007). Epilepsy and migraine in a patient with Urbach-Wiethe Disease. *Seizure, 16*(5), 465-468.

Clark, L., Cools, R., & Robbins, T. W. (2004). The neuropsychology of ventral prefrontal cortex: decision-making and reversal learning. *Brain and cognition*, 41-53.

Cohen, J. D., & Aston-Jones, G. (2005). Cognitive neuroscience: decision amid uncertainty. *Nature*, 471.

Collins, A. G., & Frank, M. J. (2012). How much of reinforcement learning is working memory, not reinforcement learning? A behavioral, computational, and neurogenetic analysis. *European Journal of Neuroscience, 35*(7), 1024-1035.

Conti, R., & Arnone, J. (2015). Neuropsychiatric symptoms of Urbach-Wiethe disease. *International Journal of Clinical and Experimental Neurology, 3*(2), 45-50.

Dagher, A., & Robbins, T. W. (2009). Personality, addiction, dopamine: insights from Parkinson's disease. *Neuron*, 502-510.

Davis, M., & Whalen, P. J. (2001). The amygdala: vigilance and emotion. *Molecular psychiatry, 6*(1), 13.

de Gelder, B., Terburg, D., Morgan, B., Hortensius, R., Stein, D. J., & van Honk, J. (2014). The role of human basolateral amygdala in ambiguous social threat perception. *Cortex, 52*, 28-34.

de Gelder, B., Terburg, D., Morgan, B., Hortensius, R., Stein, D., & van Honk, J. (2014). The role of human basolateral amygdala in ambiguous social threat perception. *Cortex, 52*, 28-34.

De Martino, B., Camerer, C., & Adolphs, R. (2010). Amygdala damage eliminates monetary loss aversion. *Proceedings of the National Academy of Sciences, 107*(8), 3788-3792.

De Quervain, D. J., Fischbacher, U., Treyer, V., & Schellhammer, M. (2004). The neural basis of altruistic punishment. *Science*, 1254.

Eickhoff, S. B., Stephan, K. E., Mohlberg, H., Grefkes, C., Fink, G. R., Amunts, K., & Zilles, K. (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage, 25*(4), 1325-1335.

Eisenberg, N. (1992). *The Caring Child.* Cambridge, MA: Harvard University Press.

Eisenberg, N., Fabes, R., & Spinrad, T. (2006). *Prosocial development. Handbook of Child Psychology: Social, Emotional, and Personality Development.* (e. E. N, Ed.) Hoboken, NJ: Wiley.

Eisenegger, C., Naef, M., Linssen, A., Clark, L., Gandamaneni, P., Muller, U., & Robbins, T. (2014). Role of dopamine D2 receptors in human reinforcement learning. *Neuropsychopharmacology, 39*, 2366-2375.

Esber, G., & Holland, P. (2014). The basolateral amygdala is necessary for negative prediction errors to enhance cue salience, but not to produce conditioned inhibition. *European Journal of Neuroscience, 40*(9), 3328-3337.

Fehr, E., & Camerer, F. (2007). Social neuroeconomics: The neural circuitry of social preferences. *Trends in Cognitive Science, 10*(11), 419–427.

Feinstein, J., Buzza, C., Hurlemann, R., Follmer, R., Dahdaleh, N., W.H., C., . . . Wemmie, J. (2013). Fear and panic in humans with bilateral amygdala damage. *Nature Neuroscience, 16*, 270-272.

Fellows, L. K. (2007). The role of orbitofrontal cortex in decision making: a component process account. *Annals of the New York Academy of Sciences*, 421-430.

Fellows, L. K., & Farah, M. J. (2007). The role of ventromedial prefrontal cortex in decision making: judgment under uncertainty or judgment per se? *Cerebral corte*, 2669-2674.

Floresco, S., & Tse, M. (2007). Dopaminergic regulation of inhibitory and excitatory transmission in the basolateral amygdala-prefrontal cortical pathway. *Journal of Neuroscience, 27*, 2045–2057.

Gallagher, M., & Schoenbaum, G. (1999). Functions of the amygdala and related forebrain areas in attention and cognition. *Annals of the New York Academy of Sciences, 877*(1), 397-411.

Garcia, R., Vouimba, R., Baudry, M., & Thompson, R. (1999). The amygdala modulates prefrontal cortex activity relative to conditioned fear. *Nature, 402*(6759), 294.

Ghashghaei, H., & Barbas, H. (2002). Pathways for emotion: interactions of prefrontal and anterior temporal pathways in the amygdala of the rhesus monkey. *Neuroscience, 115*(4), 1261-1279.

Ghods-Sharifi, S., St.Onge, J., & Floresco, S. (2009). Fundamental Contribution by the Basolateral Amygdala to Different Forms of Decision Making. *Journal of Neuroscience, 29*(16), 5251-5259.

Goncalves, F., de Melo, M., de L Matos, V., Barra, F., & Figueroa, R. (2010). Amygdalae and striatum calcifications in lipoid proteinosis. *American Journal of Neuroroadiology, 31*, 88-90.

Graeff, F. G., & Del-Ben, C. M. (2008). Neurobiology of panic disorder: from animal models to brain neuroimaging. *Neuroscience & Biobehavioral Reviews, 32*(7), 1326-1335.

Gündüz, Ö., Şahiner, N., Atasoy, P., & Şenyücel, Ç. (2012). Acitretin Treatment for Lipoid Proteinosis. *Case Reports in Dermatological Medicine*, 1-4.

Gupta, R., Koscik, T. R., Bechara, A., & Tranel, D. (2011). The amygdala and decision-making. *Neuropsychologia, 49*(4), 760-766.

Hamada, T., McLean, W., Ramsay, M., Ashton, G., Nanda, A., Jenkins, T., & McGrath, J. A. (2002). Lipoid proteinosis maps to 1q21 and is caused by mutations in the extracellular matrix protein 1 gene (ECM1). *Human Molecular Genetics, 11*, 833–84.

Hamada, T., Wessagowit, V., South, A. A., Chan, I., Oyama, N., Siriwattana, A., & McGrath, J. (2003). Extracellular matrix 1 gene (ECM1) mutations in lipoid proteinosis and genotype-phenotype correlation. *Journal of Investigative Dermatology, 120*, 345-350.

Hariri, A. R., Tessitore, A., Mattay, V. S., Fera, F., & Weinberger, D. R. (2002). The amygdala response to emotional stimuli: a comparison of faces and scenes. *Neuroimage, 17*(1), 317-323.

Haruno, M., Kimura, M., & Frith, C. D. (2014). Activity in the nucleus accumbens and amygdala underlies individual differences in prosocial and individualistic economic choices. *Journal of Cognitive Neuroscience, 26*(8), 1861-1870.

Hauber, W., & Sommer, S. (2009). Prefrontostriatal circuitry regulates effort-related decision making. *Cerebral Cortex, 19*, 2240.

Heimer, L., Harlan, R., Alheid, G., Garcia, M., & De Olmos, J. (1997). Substantia innominata: a notion which impedes clinical–anatomical correlations in neuropsychiatric disorders. *Neuroscience, 76*(4), 957-1006.

Henri-Bhargava, A., Simioni, A., & Fellows, L. K. (2012). Ventromedial frontal lobe damage disrupts the accuracy, but not the speed, of value-based preference judgments. *Neuropsychologia*, 1536-1542.

Henrich, J., McElreath, R., Barr, A., Ensminger, J., Barrett, C., Bolyanatz, A., & Lesorogol, C. (2006). Costly punishment across human societies. *Science, 312*(5781), 1767-1770.

Hernandez-Lallement, J., van Wingerden, M., Schäble, S., & Kalenscher, T. (2016). Basolateral amygdala lesions abolish mutual reward preferences in rats. *Neurobiology of learning and memory, 127*, 1-9.

Heyl, T. (1970). Geological study of lipoid proteinosis in South Africa. *British journal of dermatology, 83*, 338-340.

Hofer, P. (1973). Urbach-Wiethe Diesease (lipoglycoproteinosis; lipoid proteinosis; hyalinosis cutis et mucosae): a review. *Acta Derm Venereol, 53(Suppl 71)*, 1-52.

Hollis, M., & Nell, E. (1975). *Rational Economic Man: A Philosophical Critique of Neo-Classical Economics.* Cambridge, UK: Cambridge Univ Press.

Holme, S., Lenane, P., & Krafchik, B. (2005). What syndrome is this? Urbach-Wiethe Syndrome (Lipoid Proeteinosis). *Pediatric Dermatology, 22*(3), 266-267.

Hortensius, R. T. (2016). The role of the basolateral amygdala in the perception of faces in natural contexts. *Philos. Trans. Soc. Lond. B. Biol. Sci*, 371.

Hurlemann, R., Patin, A., Onur, O., Cohen, M., Baumgartner, T., & Metzler, S. (2010). Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *Journal of Neuroscience, 30*, 4999–5007.

Hurlemann, R., Schlaepfer, T. E., Matusch, A., Reich, H., Shah, N. J., Zilles, K., & Bauer, A. (2009). Reduced 5-HT2A receptor signaling following selective bilateral amygdala damage. *Social cognitive and affective neuroscience, 4*(1), 79-84.

Ildefonso, M., Bringas, C., Malaina, I., Fedetz, M., Carrasco-Pujante, J., Morales, M., & Pérez-Yarza, G. (2019). Evidence of conditioned behavior in amoebae. *Nature communications, 10*(1), 1-12.

Izquierdo, A., & Murray, E. (2007). Selective bilateral amygdala lesions in rhesus monkeys fail to disrupt object reversal learning. *Journal of Neuroscience, 27*, 1054 –1062.

Izquierdo, A., Darling, C., Manos, N., Pozos, H., Kim, C., Ostrander, S., & Rudebeck, P. H. (2013). Basolateral amygdala lesions facilitate reward choices after negative feedback in rats. *Journal of Neuroscience, 33*(9), 4105-4109.

Jovanovic, T., & Ressler, K. (2010). How the neurocircuitry and genetics of fear inhibition may inform our understanding of PTSD. *Am J Psychiatry, 167*, 648–662.

Kachewar, S., Singh, B., Sesane, A., & Bhadane, S. (2011). Full blown case of lipoid proteinosis. *Medical Journal of the Armed forces of India, 67*, 90-91.

Kapp, B., Whalen, P., Supple, W., & Pascoe, J. (1992). Amygdaloid contributions to conditioned arousal and sensory processing. In A. J.P., *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (pp. 229-254). New York: Wiley-Liss.

Kapur, N. (1996). Paradoxical Functional facilitaion in brain-behaviour research. A critical review. *Brain, 119*, 1775-1790.

Klumpers, F., Morgan, B., Terburg, D., Stein, D., & van Honk, J. (2015). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdala damage. *Social Cognitive and Affective Neuroscience, 10*, 1161-1168.

Klumpers, F., Morgan, B., Terburg, D., Stein, D., & van Honk, J. (2015). Impaired acquisition of classically conditioned fear-potentiated startle reflexes in humans with focal bilateral basolateral amygdale damage. *Soc Cogn Affect Neurosci, 10*, 1161-1168.

Koen, N., Fourie, J., Terburg, D., Stoop, R., Morgan, B., Stein, D., & van Honk, J. (2016). Translational neuroscience of basolateral amygdala lesions: Studies of urbach-wiethe disease. *Journal of Neuroscience Research, 94*, 504-512.

Koenigs, M., & Tranel, D. (2007). Irrational economic decision-making after ventromedial prefrontal damage: evidence from the Ultimatum Game. *Journal of Neuroscience*, 951-956.

Kutschera, U., & Briggs, W. R. (2015). Phototropic solar tracking in sunflower plants: an integrative perspective. *Annals of botany, 117*(1), 1-8.

LeDoux, J. (2007). The amygdala. *Current biology, 17*(20), 868-874.

Lee, D., & Seo, H. (2016). Neural basis of strategic decision making. *Trends in Neuroscience, 39*(1), 40-48.

Lockwood, P. L., Apps, M. A., Valton, V., Viding, E., & Roiser, J. P. (2016). Neurocomputational mechanisms of prosocial learning and links to empathy. *Proceedings of the National Academy of Science, 113*(35), 9763-9768.

Macedo, C. E., Cuadra, G., Molina, V., & Brandão, M. L. (2005). Aversive stimulation of the inferior colliculus changes dopamine and serotonin extracellular levels in the frontal cortex: modulation by the basolateral nucleus of amygdala. *Synapse, 55*(1), 58-66.

Martinez, R. C., de Oliveira, A. R., & Brandão, M. L. (2007). Serotonergic mechanisms in the basolateral amygdala differentially regulate the conditioned and unconditioned fear

organized in the periaqueductal gray. *European Neuropsychopharmacology, 17*(11), 717-724.

Matthies, S., Rusch, N., & Weber, M. (2012). Small amygdala- high aggression? The role of the amygdala in modulating aggression in healthy subjects. *World Journal of Biological Psychiatry, 13*(1), 75-78.

Meeren, H. K., van Heijnsbergen, C. C., & de Gelder, B. (2005). Rapid perceptual integration of facial expression and emotional body language. *Proceedings of the National Academy of Sciences, 102*(45), 16518-16523.

Mobbs, D., Petrovic, P., Marchant, J. L., Hassabis, D., Weiskopf, N., Seymour, B., & Frith, C. D. (2007). When fear is near: threat imminence elicits prefrontal-periaqueductal gray shifts in humans. *Science, 317*(5841), 1079-1083.

Moll, J., & Schulkin, J. (2009). Social attachment and aversion in human moral cognition. *Neuroscience and Biobehaviour Review, 33*(3), 456–465.

Morgan, B., Terburg, D., Thornton, H. B., Stein, D. J., & van Honk, J. (2012). Paradoxical facilitation of working memory after basolateral amygdala damage. *PLoS One, 7*(6), e38116.

Nanda, A., Alsaleh, Q., Al-Sabah, H., Ali, A., & Anim, J. (2001). Lipoid Proteinosis: Report of four siblings and brief review of the literature. *Peadeatric Dermatology, 18*(1), 21-26.

National Institute of Neurological Disorders and Stroke. (2016, June). *Lipoid Proteinosis information page*. Retrieved from National Institute of Neurological Disorders and Stroke: https://www.ninds.nih.gov/Disorders/All-Disorders/Lipoid-Proteinosis-Information-Page

Oyama, N., & Merregaert, J. (2017). The Extracellular Matrix Protein 1 (ECM1) in Molecular-Based Skin Biology. In M. K. Farage M., *Textbook of Aging Skin.* Heidelberg: Springer.

Parida, J. R., Misra, D. P., & Agarwal, V. (2015). Urbach-Wiethe syndrome. *BMJ case reports*, bcr2015212443.

Paulus, M. (2007). Decision-making dysfunctions in psychiatry - Altered homeostatic processing? *Science, 318*(5850), 602-605.

Rand, D., Greene, J., & Nowak, M. (2012). Spontaneous giving and calculated greed. *Nature, 489*(7416), 427–430.

Rilling, J. K., & Sanfey, A. G. (2011). The neuroscience of social decision-making. *Annual review of psychology, 62*, 23-48.

Rilling, J., & Sanfey, A. (2011). The neuroscience of social decision-making. *Annual Review of Psychology, 68*, 23-48.

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural neurology, 12*(4), 191-200.

Rosenberger, L., Eisenegger, C., Naef, M., Terburg, D., Fourie, J., Stein, D., & Van Honk, J. (2019). The human basolateral amygdala is crucial for social experiential learning. *Current Biology, 29*(12).

Rudebeck, P. H., & Murray, E. A. (2014). The orbitofrontal oracle: cortical mechanisms for the prediction and evaluation of specific behavioral outcomes. *Neuron*, 1143-1156.

Rudebeck, P., & Murray, E. (2008). Amygdala and orbitofrontal cortex lesions differentially influence choices during object reversal learning. *Journal of Neuroscience, 28*, 8338 –8343.

Ruff, C., & Fehr, E. (2014). The neurobiology of rewards and values in social decision making. *Nature Reviews Neuroscience, 15*(8), 549–562.

Saddoris, M., Gallagher, M., & Schoenbaum, G. (2005). Rapid associative encoding in basolateral amygdala depends on connections with orbitofrontal cortex. *Neuron, 46*(2), 321-331.

Sah, P., Faber, E. L., Lopez de Armentia, M., & Power, J. (2003). The amygdaloid complex: anatomy and physiology. *Physiological reviews, 83*(3), 803-834.

Sanfey, A. G. (2007). Social decision-making: insights from game theory and neuroscience. *Science, 318*(5850), 598-602.

Shadlen, M. N., & Kiani, R. (2013). Decision making as a window on cognition. *Neuron, 80*(3), 791–806.

Shi, C., & Cassell, M. (1998). Cortical, thalamic, and amygdaloid connections of the anterior and posterior insular cortices. *Journal of Comparative Neurology, 399*(4), 440-468.

Siebert, M., Markowitsch, H., & Bartel, P. (2013). Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain, 126*, 2627–2637.

St Onge, J., & Floresco, S. (2009). Dopaminergic modulation of risk-based decision making. *Neuropsychopharmacology, 34*, 681–697.

Stine, O. C., & Smith, K. D. (1990). The estimation of selection coefficients in Afrikaners: Huntington disease, porphyria variegata, and lipoid proteinosis. *American Journal of Human Genetics, 46*, 452–458.

Terburg, D., Morgan, B. E., Montoya, E. R., Hooge, I. T., Thornton, H. B., Hariri, A. R., & Van Honk, J. (2012). Hypervigilance for fear after basolateral amygdala damage in humans. *Translational Psychiatry, 2*(5), e115.

Terburg, D., Scheggia, D., Del Rio, R. T., Klumpers, F., Ciobanu, A. C., Morgan, B., & de Gelder, B. (2018). The basolateral amygdala is essential for rapid escape: A human and rodent study. *Cell, 175*(3), 723-735.

Thornton, H. B., Nel, D., Thornton, D., van Honk, J., Baker, G. A., & Stein, D. J. (2008). The neuropsychiatry and neuropsychology of lipoid proteinosis. *The Journal of Neuropsychiatry and Clinical Neurosciences, 20*, 86–92.

Tranel, D., & Hyman, B. (1990). Neuropsychological correlates of bilateral amygdala damage. *Arch Neurol, 47*, 349-355.

Tremblay, M., Cocker, P. J., Hosking, J. G., Zeeb, F. D., Rogers, R. D., & Winstanley, C. A. (2014). Dissociable effects of basolateral amygdala lesions on decision making biases in rats when loss or gain is emphasized. *Cognitive, Affective, & Behavioral Neuroscience, 14*(4), 1184-1195.

Tye KM, e. a. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature, 471*(7338), 358–362.

Tye, K. M., Prakash, R., Kim, S. Y., Fenno, L. E., Grosenick, L., Zarabi, H., & Deisseroth, K. (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. *Nature, 471,*(7338), 358.

Urbach, E., & Wiethe, C. (1929). Lipoidosis cutis et mucosae. *Virchows Arch Pathol Anat Physiol Klin Med, 273*, 285-319.

Vahidnezhad, H., Youssefian, L., & Uitto, J. (2016). Lipoid Proteinosis. *Gene reviews*.

Van Honk, J. (2009). Neuroendocrine manipulation of the sexually dimorphic human social brain. In E. Harmon-Jones, & J. Beer, *Methods in social neuroscience* (pp. 45-69). New york: Guilford Press.

Van Honk, J., Eisenegger, C., Terburg, D., Stein, D., & Morgan, B. (2013). Generous economic investments after basolateral amygdala damage. *Proceedings of the Natural Adacemy of Sciences, 110*(7), 2506-2510.

van Honk, J., Peper, J. S., & Schutter, D. J. (2005). Testosterone reduces unconscious fear but not consciously experienced anxiety: implications for the disorders of fear and anxiety. *Biological psychiatry, 58*(3), 218-225.

van Honk, J., Terburg, D., Thornton, H., Stein, D., & Morgan, B. (2016). Consequences of selective bilateral lesions to the basolateral amygdala in humans. In D. A. Amaral, *Living without an amygdala.* Guilford Press.

Van Hougenhouck-Tulleken, W., Chan, I., Hamada, T., Thornton, H., Jenkins, T., McLean, W. H., & Ramsay, M. (2004). Clinical and molecular characterization of lipoid proteinosis in Namaqualand, South Africa. *British Journal of Dermatology, 151*(2), 413-423.

Wallis, J. (2012). Cross-species studies of orbitofrontal cortex and value-based decision-making. *Nature Neuroscience, 12*, 13–19.

Wechsler, D. (2011). WASI -II: Wechsler abbreviated scale of intelligence - second edition. *WASI.*

Wiest, G., Lehner-Baumgartner, F., & Baumgartner, C. (2006). Panic attacks in an individual with bilateral selective lesions of the amygdala. *Arch Neurol, 63*(12), 1798-1801.

Xu, W., Wang, L., Zhang, L., Han, D., & Zhang, L. (2010). Otolaryngological manifestations and genetic characteristics of lipoid proteinosis. *Ann Otol Rhinol Laryngol, 119*, 767-71.

Yacubian, J., Gläscher, J., Schroeder, K., Sommer, T., Braus, D. F., & Büchel, C. (2006). Dissociable systems for gain-and loss-related value predictions and errors of prediction in the human brain. *Journal of Neuroscience, 26*(37), 9530-9537.

Yun, R. J., Krystal, J. H., & Mathalon, D. H. (2010). Working memory overload: fronto-limbic interactions and effects on subsequent working memory function. *Brain imaging and behavior, 4*(1), 96-108.