

**THE RELATIONSHIP BETWEEN TEMPERAMENT AND SERUM SEROTONIN
CONCENTRATION IN MIGRAINE WITHOUT AURA**

by

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18 May 2016

DECLARATION

Student number: 5331-957-5

I declare that "*The relationship between temperament and serum serotonin concentration in migraine without aura*" is my own work and that all sources I have used or quoted have been indicated and acknowledged by means of complete references.



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Date

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ABSTRACT

Cloninger's Psychobiological Theory of Personality proposes four temperament dimensions, each underpinned by a different neurotransmitter system. The serotonergic system is purportedly linked to Harm Avoidance (HA). The aim of this study was to explore the relationship between HA and serotonin in migraine without aura (MO). A second aim was to explore the personality profile of MO patients. Sixty-six participants completed an online questionnaire and donated blood samples. Results indicated no significant association between HA and serotonin and a significant relationship between MO and HA. This study indicates that both Cloninger's Psychobiological Theory of Personality and the Tridimensional Personality Questionnaire used for its assessment have value in South African personality research. In addition, the findings of the study reveal support for personality influences on the processes involved in migraine. This not only produces worthwhile avenues of research but also an alternative perspective for clinical practice.

Key words: Enzyme-linked Immunosorbent Assay, migraine without aura, personality, Psychobiological Theory of Personality, serotonin, Tridimensional Personality Questionnaire

LIST OF ABBREVIATIONS

5-HIAA	5-Hydroxy-indoleacetic acid
5-HT	5-Hydroxytryptamine (also known as serotonin)
16PF	16-Personality Factor Questionnaire
ACC	Anterior cingulate cortex
ASI	Anxiety Sensitivity Index
AUC	Area under the Curve
BAS	Behavioural Approach System
BDI	Beck Depression Inventory
BI	Binding indices
BIS	Behavioural Inhibition System
BP-I	Bipolar I
BP-II	Bipolar II
CNS	Central nervous system
CO	Cooperativeness
CORT	Cortisol hormone
CV	Coefficient of variation
DPFC	Dorsal prefrontal cortex
ELISA	Enzyme-linked immunosorbent assay
EPI	Eysenck Personality Inventory
EPQ	Eysenck Personality Questionnaire
FFFS	Fight-Flight-Freezing system
FFM	Five-Factor Model
FFS	Fight-Flight System

HA	Harm Avoidance
Ham-D17	17-item Hamilton Depression Rating Scale
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
MA	Migraine with aura
MO	Migraine without aura
NEO-PI-R	The Revised NEO Personality Inventory
NRF	National Research Foundation
NS	Novelty Seeking
P	Persistence
PCS	Pain Catastrophizing Scale
PDQ-R	Personality Disorders Questionnaire-Revised
PEN	Three-factor model of personality by Eysenck: Extraversion-Introversion, Neuroticism-Stability, and Psychoticism-Superego Function
PET	Positron emission tomography
PFC	Prefrontal cortex
PMO	Probable migraine without aura
PNRS	Pain Numerical Rating Scale
PRL	Prolactin hormone
PTN	Painful trigeminal neuropathy
RAS	Reticular Activating System
RD	Reward Dependence
RST	Reinforcement Sensitivity Theory
SACS	Strategic Approach to Coping Scale

SAD	Social anxiety disorder
SD	Self-directedness
SNP	Single nucleotide polymorphism
SSRI	Selective serotonin reuptake inhibitor
ST	Self-transcendence
TCI	Temperament and Character Inventory
TMD	Temporomandibular disorder
TPQ	Tridimensional Personality Questionnaire
TTH	Tension-type headache
VD	Vascular disease
ZKPQ	Zuckerman-Kuhlman Personality Questionnaire

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NEUROANATOMY OVERVIEW

In order to facilitate the reading of this dissertation, an overview of relevant neuroanatomy is provided. A general overview of brain structure is summarised in table format. A brief discussion is presented on the locations and functions. Thereafter, the relevant locations and functions of the structures, systems, and pathways are briefly presented in table format. By providing this additional information it is anticipated that the reader will be better able to focus on the arguments made within the dissertation which refer to the neuroanatomical structures already described.

Table A indicates a general overview of brain structure. In the first column of Table A, the main three brain structures are indicated: the hindbrain (rhombencephalon), the midbrain (mesencephalon), and the forebrain (prosencephalon) (Kalat, 2014; Waxman, 2010). This and the accompanying text provides a holistic understanding of the brain. The ensuing columns indicate the more specialised brain areas within the main three structures (Kalat, 2014; Roxo, Franceschini, Zubarán, Kleber, & Sander, 2011; Waxman, 2010). Not all areas are presented; only the structures relevant to this dissertation are included so as to avoid unnecessary complication. Although each area can be delineated for the purposes of simplicity and brevity, the brain is too complicated a system to present as a collection of parts. Each area and system influences another, with many pathways. This should be kept in mind during this section.

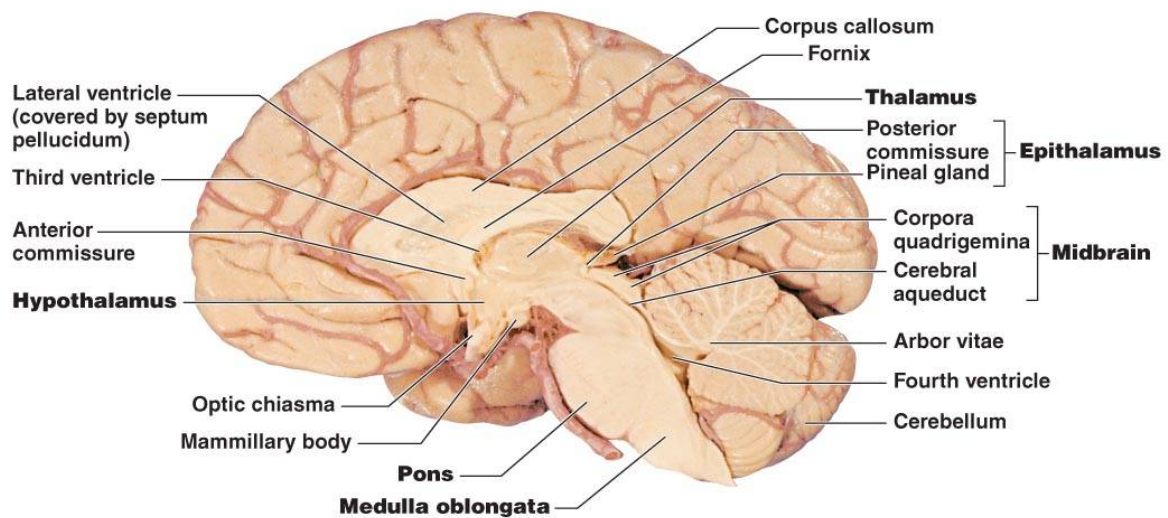
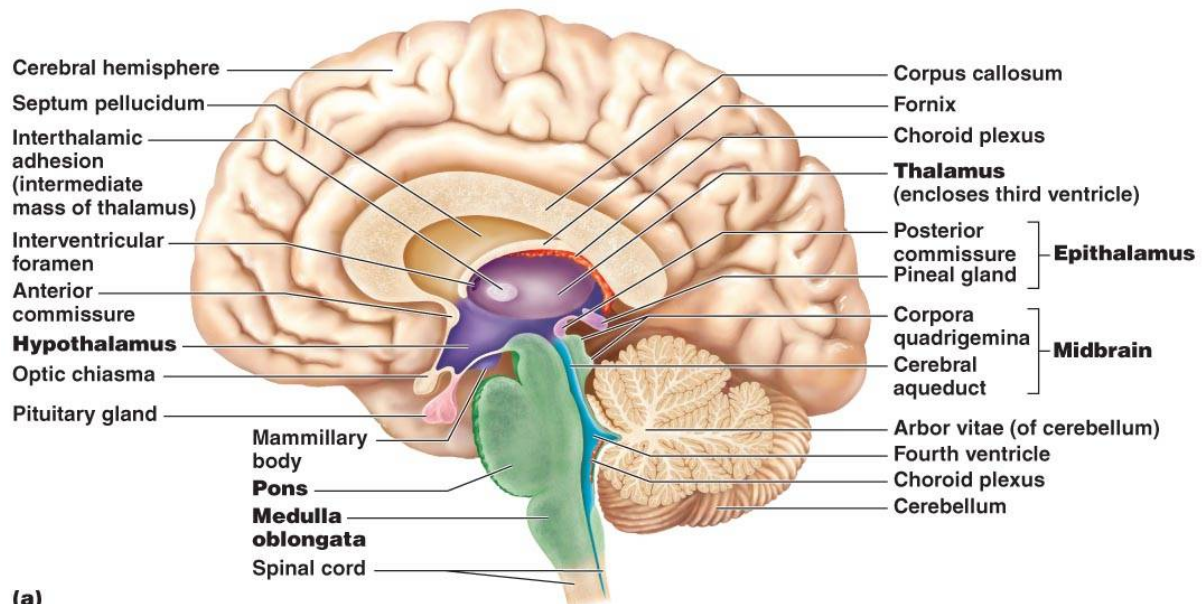
The **hindbrain** consists of the cerebellum, the pons, and the medulla oblongata (Kalat, 2014). The **midbrain** is, as the name suggests, located in the middle of the brain and consists of the tectum, the tegmentum, the ventricular mesocoelia, and the cerebral peduncles

(Roxo et al., 2011). The pons, medulla oblongata, the midbrain, and some forebrain structures, comprise the brain stem (Kalat, 2014; Waxman, 2010) and are indicated in Figure A (Marieb & Hoehn, 2013). The brain stem is the connection between the spinal cord and the rest of the brain (Roxo et al., 2011; Waxman, 2010). In addition to containing nuclei which are essential for survival, the brain stem serves as a pathway for ascending and descending neural tracts between the lower and higher brain centres (Waxman, 2010). The cerebellum is located dorsal to the brain stem and plays a vital role in motor coordination (Kalat, 2014; Waxman, 2010). The cerebellum may also have functions related to attention and timing (Kalat, 2014).

The **forebrain** is composed of structures developed from the diencephalon and telencephalon, as indicated in Table A (Kalat, 2014; Roxo et al., 2011; Waxman, 2010). The diencephalon matures into the thalamus, metathalamus, hypothalamus, subthalamus, epithalamus, and pretectum (Roxo et al., 2011; Waxman, 2010). The thalamus, hypothalamus, and epithalamus are indicated in Figure A (Marieb & Hoehn, 2013). The telencephalon develops into the cerebrum, consisting of the right and left cerebral hemispheres each parsed into five lobes (occipital, temporal, parietal, frontal, and the hidden insula) and connected by the corpus callosum (Izac, Suzette, & Izac, 2006; Kalat, 2014; Roxo et al., 2011; Waxman, 2010).

The outer layer of the cerebrum is the cortex and is composed of the nuclei of brain cells whereas the thick inner layer, including the corpus callosum, is comprised of white matter fibers which form connections throughout the brain to transmit information (Izac et al., 2006). The cerebral cortex, cerebral white matter, and corpus callosum are indicated in Figure

B (Marieb & Hoehn, 2013). The commissures, basal ganglia, nuclei of Meynert, and the septal nuclei also develop from the telencephalon (Kalat, 2014; Roxo et al., 2011; Waxman, 2010).



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Figure A. Illustration of the cross-sectional view of the brain. Reprinted from *Human Anatomy & Physiology* (9th ed.) (p. 440), by E. N. Marieb and K. Hoehn, 2013, Upper Saddle River, NJ: Pearson Education, Inc. © 2013 by Pearson Education, Inc. Reprinted with permission.

The brain is a network where each part has a unique function(s), while each part also works together with other structures in larger processes. An attempt has been made within Table B to discuss each part separately, as the confines of a dissertation are limited, but the brain is better understood as a system. Therefore, reference has been made within the table where applicable to a structure's involvement in systems, connected areas, connecting pathways, and projections. Table C goes on to describe the specific structures and functions of important systems in more detail.

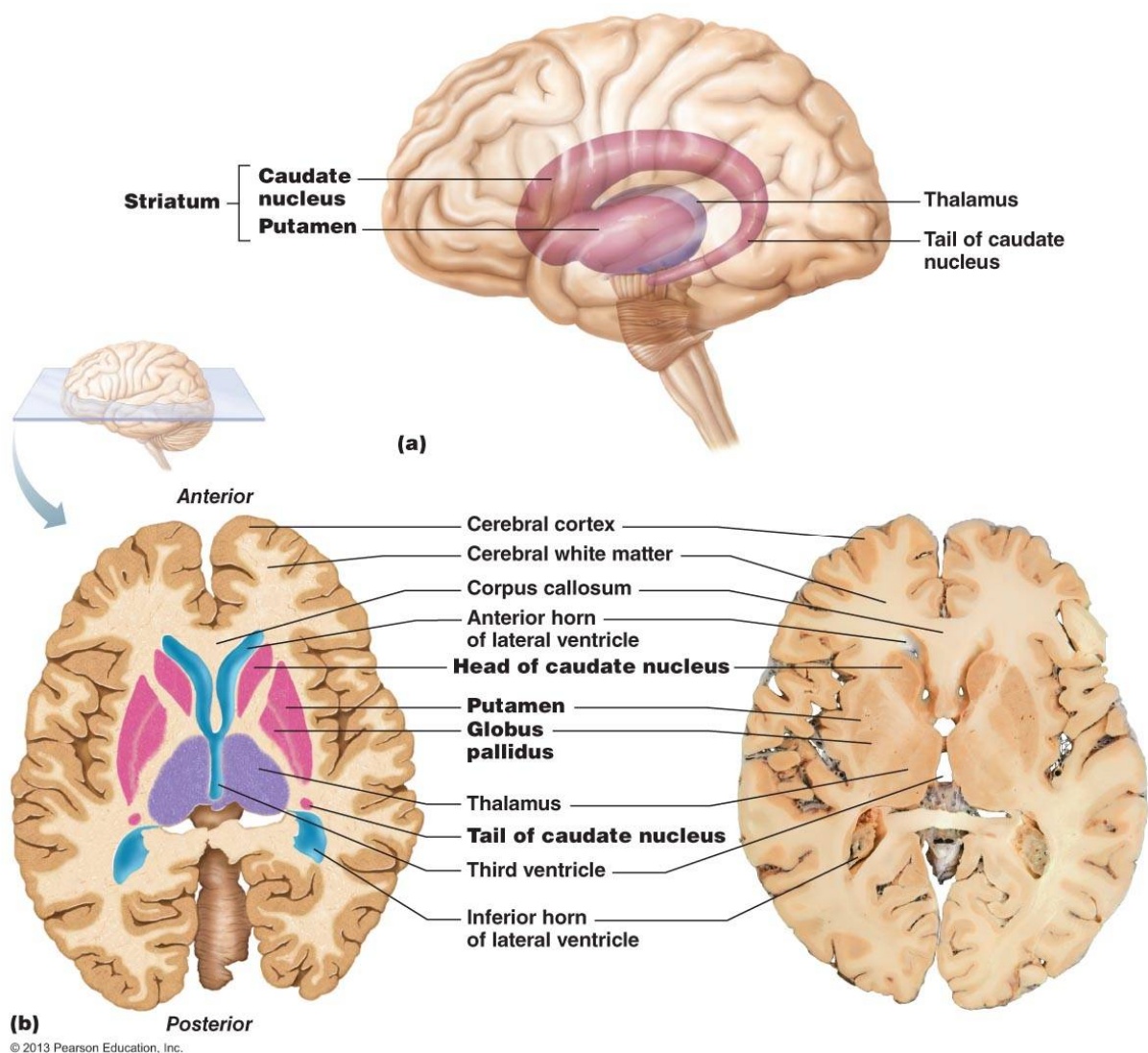


Figure B. Illustration of the horizontal view of the brain. Reprinted from Human Anatomy & Physiology (9th ed.) (p. 439), by E. N. Marieb and K. Hoehn, 2013, Upper Saddle River, NJ: Pearson Education, Inc. © 2013 by Pearson Education, Inc. Reprinted with permission.

Table A

Overview of brain structures

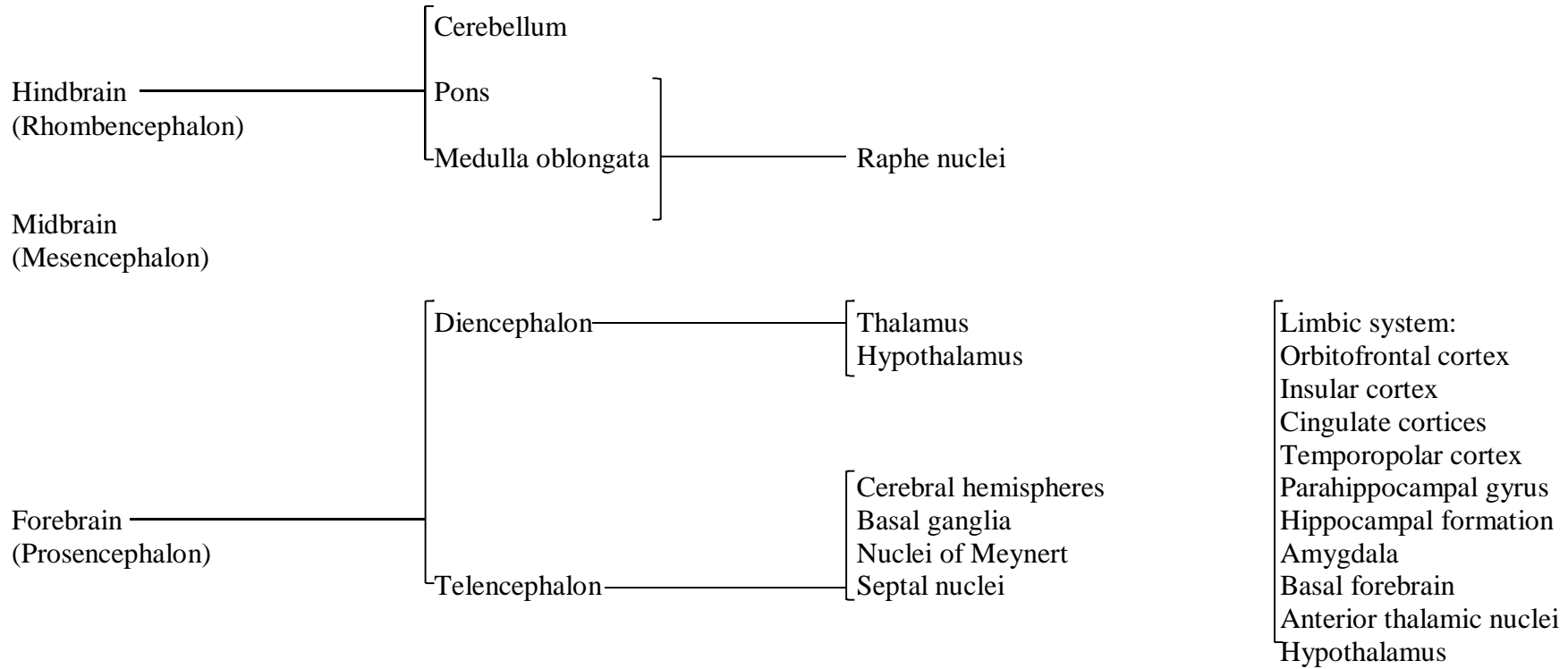


Table B

Descriptions of specific structures and their functions

Structure	Brief description of brain area and function(s)
Amygdala	<p>The amygdala is located in the temporal lobe (Schumann, Bauman, & Amaral, 2011) of the left and right cerebral hemispheres. Also known as the amygdaloid complex (AC), the amygdala is composed of thirteen nuclei which are connected both to each other and various areas of the brain (Pabba, 2013; Schumann et al., 2011). Due to these wide connections, the amygdala processes many types of information including inputs from the gut and viscera, somatosensory system, auditory system, visual system, cortex, thalamus, hypothalamus, brainstem, and olfactory system (Pabba, 2013) and thereby mediates various functions including learning the emotional significance of environmental stimuli in relation to fear conditioning, modulating social behaviour, sexual behaviour, and olfaction (Schumann et al., 2011). The amygdala is a central part of the limbic system (Sokolowski & Corbin, 2012).</p>
Anterior cingulate cortex	<p>This area refers to a part of the frontal midline cortex (Holroyd & Yeung, 2012; Sanders, Gallup, Heinsen, Hof, & Schmitz, 2002) and integrates cognitive and emotional processes to motivate goal-directed behaviour (Fornito et al., 2009; Holroyd & Yeung, 2012). The anterior cingulate cortex is part of the brain's limbic system (Bush, Luu, & Posner, 2000; Feinstein et al., 2010).</p>
Basal nucleus of Meynert	<p>The basal nucleus of Meynert (BNM) is located in the basal forebrain below the basal ganglia (Li et al., 2014; Waxman, 2010) and sends widespread cholinergic projections, which use acetylcholine as a neurotransmitter, throughout the cerebral cortex (Husain & Mehta, 2011; Li et al., 2014; Waxman, 2010). The BNM plays a role in attention, learning and memory, and additional cognitive functions (Li et al., 2014).</p>

Hypothalamus	This is a small gray matter structure situated below and in front of the thalamus (Izac et al., 2006; Kalat, 2014; Waxman, 2010) and is indicated in Figure 1. Various hormones and factors required for homeostasis and correct growth and development are produced and released by the hypothalamus through its vascular association with the pituitary gland (Izac et al., 2006). Homeostatic functions and behaviours with which it is involved include eating behaviour, autonomic functions, heart rate and blood pressure, body temperature regulation, water balance, anterior pituitary function, sleep cycles, sexual functions, and expression of emotion (Alvarez-Bolado, Grinevich, & Puelles, 2015; Izac et al., 2006; Waxman, 2010).
Locus coeruleus	This area of the brain is located within the pons and is the main producer of norepinephrine (Husain & Mehta, 2011; Joe, Fernandez, & Roozendaal, 2011; Waxman, 2010). Noradrenergic neurons then project to innervate the cerebral cortex (Husain & Mehta, 2011). Noradrenergic projections play a role in several processes including stress response, learning, reward, depression, as well as behavioural inhibition and non-reward (Stone, Lin, Sarfraz, & Quartermain, 2011).
Periaqueductal grey matter (PAG)	This area is located in the midbrain (Buhle <i>et al.</i> , 2013; Waxman, 2010) and contains descending tracts as well as cells that produce endorphins, suppressing pain (Waxman, 2010).
Posterior cingulate cortex	This refers to the portion of cingulate cortex behind the central sulcus and is connected to areas involved in attention, learning and motivation, and memory (Pearson, Heilbronner, Barack, Hayden, & Platt, 2011). Additionally, it is part of the limbic system (Feinstein et al., 2010).
Raphe nuclei	The raphe nuclei are located in the brainstem , specifically in the pons, the medulla oblongata (Waxman, 2010), and the midbrain (Fischer, Jocham, & Ullsperger, 2015). The raphe nuclei contain approximately half a million serotonergic cells , the vast majority of all these cells, which project to nearly all areas of the brain including the cortex, hippocampus, basal ganglia, thalamus, cerebellum, and spinal cord (Cools, Roberts, & Robbins, 2007; Fischer et al., 2015; Waxman, 2010). Functions include emotional regulation, processing reward/punishment, disregard of delays, and behavioural disinhibition (Fischer et al., 2015).

Septal nuclei

The septal nuclei receive afferents from the hippocampal formation and reticular system and sends axons to the hippocampus, hypothalamus, and midbrain. Due to involvement with several afferents and efferents, no single function can be assigned to this area although it appears to be implicated in the sensation of self-reward (Waxman, 2010).

Ventral tegmental area

The **mesolimbic dopaminergic pathway** as well as the **mesocortical pathway** begin within the ventral tegmental area (Husain & Mehta, 2011). The dopaminergic neurons from the mesolimbic pathway then innervate the **limbic system** (Alcaro, Huber, & Panksepp, 2007; Husain & Mehta, 2011).

Table C

Descriptions of specific systems and their functions

System	Brief description of brain area(s) and function(s)
Limbic system	<p>This system is involved in basic survival functions (Waxman, 2010) as well as in linking the correct behavioural response, selected from a context-specific set comprised of both innate and learned responses, to stimuli possessing emotional, social, and motivational significance (Rommelfanger & Wichmann, 2010; Sokolowski & Corbin, 2012). A consensus on the structures which comprise the limbic system has not been reached (Feinstein et al., 2010). This dissertation uses the same structures listed by Feinstein et al. (2010), namely, “the orbitofrontal cortex, insular cortex, anterior and posterior cingulate cortices, temporopolar cortex, parahippocampal gyrus, hippocampal formation, amygdala, basal forebrain, anterior thalamic nuclei, and hypothalamus” (Feinstein et al., 2010, p. 89; Waxman, 2010).</p>
Reticular activating system (RAS)	<p>The RAS located in the brainstem is a complex network of interconnected circuits of neurons, many of which are serotonergic or adrenergic (Waxman, 2010). This system receives input from the spinal cord and then relays the impulse to the thalamus and, from the thalamus, is relayed to the entire cerebral cortex (Izac et al., 2006). Without these impulses to the cortex the individual becomes comatose and therefore the RAS plays a crucial role in maintaining behavioural arousal and consciousness (Izac et al., 2006; Waxman, 2010).</p>
Septo-hippocampal system	<p>This system refers to connections from the medial septum to the hippocampus and is mediated by different types of neurons including cholinergic, GABAergic and glutamatergic. Its functions are related to memory formation (Tsanov, 2015).</p>

CHAPTER 1: INTRODUCTION AND OVERVIEW

In this chapter, the reader is introduced to migraine and the various influences it has on all aspects of an individuals' life. Further, reference is made to a biopsychosocial perspective of migraine which includes possible relationships with factors such as temperament and the serotonin neurotransmitter. Following this introduction, the rationale for the study is presented which highlights the conflicting results of previous studies as well as both the practical and theoretical applications of the results of the current study. The problem statement and a synopsis of how the research aims, research questions, and hypotheses were developed are then given. Although the latter are summarised in this section (section 1.3), the reader should note that the aims, questions, and hypotheses are presented in full in Chapter 4: Research Methodology (section 4.1). A brief summary of the research design and method are described and, lastly, the structure of the rest of the chapters is addressed.

Migraine is a common, chronic, neurological pain disorder with a high level of disability, but without a clear and determined cause (Cahill, Cook, & Pickens, 2014; Gasparini, Sutherland, & Griffiths, 2013; Schürks, Rist, & Kurth, 2011). South African statistics concur with the worldwide high prevalence, with approximately nine million South Africans suffering from migraine (Health24, 2014; Leaders in Wellness: The Business of Health, 2014; Migraine Research Institute, n.d.-b). However, migraine is not seen as a high priority medical condition despite the high prevalence and subsequent burden on patients, healthcare providers, and society (Cahill et al., 2014; Gasparini et al., 2013; Health24, 2012; Jensen & Stovner, 2008). Many migraineurs do not seek medical attention for several reasons including the perception and expectation of ineffective treatment, possible clinician indifference, and communication problems between patient and clinician. Rather than seeking the correct medical attention, many migraineurs self-diagnose and use over-the-counter

analgesics (Brandes, 2008). The habitual overuse of such drugs can lead to the development of chronic daily headache in the form of medication-overuse headache (Brandes, 2008; Jensen & Stovner, 2008). In addition, most clinicians do not realize the full impairment caused by migraine (Shaik, Hassan, Tan, & Gan, 2015) and may also underdiagnose and undertreat migraines (Brandes, 2008; Burton, Landy, Downs, Runken, & Study, 2009). There are two main subtypes of migraine, which are migraine with aura (MA) and migraine without aura (MO).

The effect a condition has on physical, emotional, and social functioning is measured by the health-related quality of life (HRQoL) (Bakar et al., 2015). The chronic pain and other symptoms associated with migraine impact the migraineurs' ability to function (Bakar et al., 2015) with migraine patients experiencing a decline of their HRQoL as well as increased comorbidity including anxiety and affective disorders (Bakar et al., 2015; Cahill et al., 2014; Cahill & Murphy, 2004; Shaik et al., 2015). The latter association is unsurprising given the lack of a clear cause for migraine despite our increasing knowledge regarding the mechanisms underlying migraine (Cahill et al., 2014). Individuals who suffer from diseases without a clear cause, also known as medically unexplained physical symptoms (MUPS), are associated with symptoms of depression and anxiety (Kolk, Schagen, & Hanewald, 2004). There are several syndromes which consist of collections of MUPS. Although previous studies have indicated biochemical and physiological abnormalities associated with the diseases, their commonality is that there are no defined changes in tissue to designate the medical condition (Katon, Sullivan, & Walker, 2011; Sharpe & Carson, 2011).

In addition to the influence on physical and mental health domains, migraine impacts social functioning. Migraineurs are at times forced to be absent from school or work,

although many attend despite struggling with headache and having lower productivity (Bakar et al., 2015; Gasparini et al., 2013; Migraine Research Institute, n.d.-a; Ozge, Aydinlar, & Tasdelen, 2015; Shaik et al., 2015). Although migraine is not specified, Health24 (2014) reports that up to one in five employees per company suffers from either acute or chronic headaches. The impairment of their ability to perform their duties (Berry, 2007; Burton et al., 2009; Health24, 2012; Raggi et al., 2012; Weiss, Bernards, & Price, 2008) has implications not only for the employees themselves, but their interactions with their colleagues and supervisors (Burton et al., 2009; Weiss et al., 2008), as well as for the company which could be faced with reduced productivity and additional costs (Burton et al., 2009; Raggi et al., 2012; Weiss et al., 2008). Migraine patients also reported more absent days for household duties, family, social and leisure activities than absent days taken for school or work. The trend to put work attendance before family time can impair these relationships (Bakar et al., 2015). Migraine therefore not only influences the individual's HRQoL but is also a burden on society.

As stated previously, migraine pathophysiology has not yet been fully elucidated and this contributes to the burden placed on migraineurs. However, several mechanisms have been identified and are currently considered to play a role. These mechanisms include those of a physiological or psychological nature as both are involved in all symptom production and perception (Katon et al., 2011). This indicates that a biopsychosocial view of migraine will assist in gaining a holistic view of the disorder and identifying potential treatments. Biologically, neurotransmitter imbalances, and the serotonin neurotransmitter system in particular, have been highlighted as a key role-player in migraine (Schürks et al., 2011). With regards to psychosocial aspects, personality could play a role in coping with pain disorders such as migraine (Katon et al., 2011). Therefore, a biopsychosocial perspective of migraine

should include a theory which takes into account both the personality of the individual and the biological mechanisms involved in migraine.

Cloninger's Psychobiological Theory of Personality includes four temperament dimensions and three character traits where the relative strength of each of the seven dimensions indicates personality (Mochcovitch, Nardi, & Cardoso, 2012; Verweij et al., 2010; Zuckerman, 1995). This dissertation focused on the four temperament dimensions, which are Harm Avoidance (HA), Novelty Seeking (NS), Reward Dependence (RD), and Persistence (P). According to Cloninger, serotonin is a key neurotransmitter in temperament (Abbate-Daga et al., 2007; Montag, 2014). Given the possible relationship between temperament and migraine (Di Piero et al., 2001; Mongini et al., 2005; Park, Han, Yang, Kim, & Lee, 2006; Sánchez-Román et al., 2007; Villani et al., 2010), it is hypothesized in this study that there are biopsychosocial components in the pathophysiology of migraine involving the serotonin system and temperament dimensions as they relate to personality (Abbate-Daga et al., 2007). This dissertation therefore sought to investigate the relationship between the four temperament dimensions identified by Cloninger and one of the neurotransmitters that underpin them: Serotonin.

1.1. Rationale

Migraineurs have demonstrated a 'migraine personality' (Gentili, Panicucci, & Guazzelli, 2005; Pompili et al., 2010) as well as a greater likelihood of developing both anxiety and depressive disorders (Antonaci et al., 2011). Further study of the various factors in this network could eventually lead to the formation of a migraine model and an

understanding of the elements in migraine development and pathophysiology. A fully effective migraine treatment could also be a much later possibility.

If a personality profile associated with an increased risk for migraine can be classified, then it follows that this information could lead to prevention of these diseases or outlining possible treatments (Boz et al., 2004). Some effective anti-migraine treatments have been, and are being, developed. However, the mechanisms underlying the action of these treatments are not fully known and they do not assist some individuals (Gasparini et al., 2013). In addition, chronic migraine can develop into medication-overuse headache when acute treatments are misused (Biagiatti, Grazi, Usai, & Gambini, 2014; Brandes, 2008; Jensen & Stovner, 2008; Rapoport, 2008). This is treated with detoxification from the medication, but patients often relapse. This deteriorating prognosis for chronic migraine patients has been related to dysfunctional personality traits (Biagiatti et al., 2014). Also, migraineurs with comorbid psychological conditions tend to take medication before the onset of symptoms, which contributes to medication overuse (Shaik et al., 2015).

Without fully understanding the processes of both migraine and treatments there will continue to be a percentage of untreatable individuals. Research taken from a biopsychosocial view of migraine will assist in its treatment as it takes into account all possible dimensions of a disease with no known cause.

One example of this is noted by Cloninger, Bayon, & Svrakic, (1998). These authors suggested that both temperament and character measures had been beneficial in predicting the response to antidepressant medication as well as to cognitive-behavioural therapy. For example, Margetić and Jakovljević (2013) reported that women with elevated HA scores

responded better to Desipramine, whilst those with high RD scores responded more effectively to Clomipramine. The authors therefore suggested that personality could be helpful in correctly matching the drug to the patient, this ability to predict effectiveness aiding clinical psychopharmacology. Understanding how traits, or their neurobiological structures, differ between individuals could also result in the development of new drugs. This could be particularly important for patients who do not respond to the currently available drugs (Margetić & Jakovljević, 2013).

In addition, personality is a complex construct and the further exploration of the interactions between the temperament dimensions of Cloninger's theory and their neurotransmitters could assist in personality research. HA is hypothesized to exert a modulatory influence on both NS and RD (Cloninger, 1987). HA is underpinned by the serotonergic system whilst NS by the dopaminergic system and RD by the noradrenergic system (Rodríguez-Cano, Beato-Fernandez, Rojo-Moreno, & Vaz-Leal, 2014). Both the dopaminergic and noradrenergic system have high levels of arousal associated with inhibition and low levels with disinhibition (Zuckerman, 1995). Interactions may occur at the level of the neurotransmitters whereby serotonin inhibits both dopamine and norepinephrine (Zuckerman, 1995). Therefore a low level of serotonin would be associated with HA, and both NS and RD would have high levels of their respective neurotransmitters, resulting in inhibition. This study would add to the literature and can be extended in further research to investigate the interactions of the neurotransmitter systems and temperament. Understanding these interactions could assist in better pain management, through treatments plans, therapy, or medication. This allows the patient a better quality of life.

Significant insight about the behaviour and treatment outcome of a patient can be gleaned from knowledge of their personality (Margetić & Jakovljević, 2013). For example, in a clinical setting, greater understanding of the regulation and dysregulation of emotion can lead to a more personalised treatment plan and have an impact on prognosis (Mochcovitch et al., 2012; Zinbarg, Uliaszek, & Adler, 2008). Furthermore, individuals at risk for the development of psychiatric disorders could be identified early and preventative measures put into effect (Ho et al., 2000; Klein, Kotov, & Bufferd, 2011; Kovacs & Lopez-Duran, 2010; Mochcovitch et al., 2012). For example, Mitsui et al. (2013) obtained results which indicated that high HA is a common temperament trait of depressive events. Perroud et al. (2013) also noted that suicide attempters had higher HA and NS and lower Self-Directedness (SD), the latter a character trait, scores than non-suicide attempters. However, past research into this area cannot make definitive recommendations regarding which treatment would be applicable for a certain personality type (Margetić & Jakovljević, 2013). Therefore further research is required into the “*personality conceptualizations as phenotype characteristics*” in order to aid the efficacy of clinical work (Margetić & Jakovljević, 2013, p. 327).

This does not only apply to patients diagnosed with psychiatric disorders. If clinicians have a greater understanding of the role of personality in well-being, they will be better able to promote health as well as reduce the effect of stressors (Cloninger & Zohar, 2011). There are several models describing personality and the clinician’s choice is important. Personality outlines a certain view which then influences the way in which a clinician understands and treats a patient (Widiger et al., 2006). It has recently been shown that high scores in the personality dimension Persistence (P), as defined in Cloninger’s Psychobiological Theory of Personality, can have both positive and negative consequences. That is, an individual scoring high in P may push herself to do well and benefit from her tenacity, but she may also strive

for perfectionism, thereby potentially creating anxiety. Due to a complex interplay between this dimension and other adaptive processes, both internal and external, high P has either positive or negative consequences for the individual depending on the interaction between these factors (Cloninger, Zohar, Hirschmann, & Dahan, 2012). Therefore, personality should be understood in its entirety to fully comprehend and support an individuals' psychological wellbeing.

1.2. Problem statement

Despite previous studies indicating a higher HA temperament score in the personality profiles of migraine patients (Di Piero et al., 2001; Mongini et al., 2005; Sánchez-Román et al., 2007), there have also been contrasting results in other studies where no such relationship was found (Boz et al., 2004; Nylander et al., 1996). The results of the current study will not be a definitive answer, but will contribute to this area of academic knowledge and provide the basis for future research within the South African migraine population.

Furthermore, the implication of the serotonin neurotransmitter in both HA and migraine indicates that the neurotransmitter could be a central factor in a system linking these factors and additional factors such as depression and anxiety. Boz et al. (2004) expected a relationship between HA and migraine because each of these two variables are associated with serotonin. However, this relationship was not indicated in their study. The current study therefore also assesses the serum serotonin concentration in migraine patients and controls to explore its possible relationship with temperament.

1.3. Summary and formation of aims, research questions, and hypotheses

The full research aims, research questions and hypotheses are presented in Chapter 4 (section 4.1), but here a description of how they came to be formed is given. The aims of this study were initially built on Cloninger's proposal in his Psychobiological Theory of Personality that temperament dimensions are underpinned by specific neurotransmitter systems (Bond, 2001). The variation exhibited amongst individuals with regards to their temperament was proposed to be a result of the differing activity levels of the neurotransmitter systems (Verweij et al., 2010). Therefore, the initial argument was that an individual's temperament was determined by his or her neurotransmitter system activity. Since temperament influences the development of emotional regulation (Fox & Calkins, 2003; Stadler et al., 2007), dysregulation of the underlying neurotransmitter systems could influence temperament to the extent that psychopathology results (Eisenberg et al., 1996; Fox & Calkins, 2003; Garland et al., 2010).

In studies investigating the specific personality profile of migraine patients an increased HA temperament score has been noted (Di Piero et al., 2001; Mongini et al., 2005; Sánchez-Román et al., 2007). Migraine has also been related to an increased risk of developing major depressive disorder (de Melo Santos et al., 2011; Kampman & Poutanen, 2011), indicating that there is the possibility that temperament is related to emotional regulation in migraine patients and/or serotonin concentration. Therefore, an aim of the study was to explore the temperament dimension distribution and serotonin concentrations in migraine patients and controls with the first research question being: Are there significant differences between the MO group and the control group in each of the measured dimensions of temperament? A relationship between migraine and HA was hypothesized. A further

research question asked: Are there significant differences between the MO group and the control group in the level of serotonin concentration? The hypothesis was made that the migraine group would have a lower serotonin concentration.

The serotonin neurotransmitter is proposed to underpin HA in Cloninger's theory. Therefore, an aim was to investigate the relationship between serum serotonin concentration and the four temperament dimensions. Here, the research question was: Is there a significant relationship between each of the measured dimensions of temperament and serotonin concentration? It was hypothesized that a significant relationship would be found between serotonin and only the HA dimension.

1.4. Summary of research design and methods

In order to best answer the research questions, a post-positivist quantitative correlation research design was used. Forty-three MO patients as well as 23 controls were recruited to participate in the study. The participants were asked to complete a biographical questionnaire, a researcher-designed headache questionnaire, and the Tridimensional Personality Questionnaire (TPQ) online. A blood donation for the purposes of Enzyme-Linked Immunosorbent Assay (ELISA) was also required in order to analyse serum serotonin neurotransmitter concentration.

1.5. Dissertation structure

Chapters 2 and 3 present the literature review of the dissertation where the relevant scholarship is discussed, critiqued, and used to formulate the arguments of the dissertation.

Chapter 2 introduces the concept of “personality” as well as differences and similarities between trait and temperament as used in personality research. This chapter discusses four prominent biologically- and/or trait-based personality theories. Chapter 2 then goes on to discuss the development of Cloninger’s Psychobiological Theory of Personality including similarities and dissimilarities to the aforementioned theories. Criticisms of Cloninger’s theory are also discussed as well as the appropriateness of using his theory in this study. The chapter then returns to temperament, as a fundamental construct in Cloninger’s theory, and its association with emotion regulation. One of the temperaments in Cloninger’s theory, HA, is then considered within the context of its relationships with both psychopathology and pain. The chapter concludes with a summary of key points.

Bearing in mind the previous discussion regarding HA, emotion regulation, and pain, Chapter 3 introduces migraine. The proposed “migraine personality” is presented as well as the diagnostic criteria for MO. A discussion follows on relationships between HA and migraine; HA and the serotonin neurotransmitter system; migraine and the serotonin neurotransmitter. Finally, it is proposed that the serotonin neurotransmitter system plays a role in both migraine and HA, thereby providing a plausible connection. The chapter once again closes with a summary of the main arguments as well as the main aims and expectations of the study in preparation for the methodology chapter.

Chapter 4 is the methodology chapter of the dissertation and is an extension of the summary provided above in Section 1.4. Chapter 5 presents the data analysis strategy and results of study. Chapter 6 provides an interpretation and discussion of the results which were presented in the previous chapter. The chapter also contains recommendations for further

research and real-life application. In addition, both the strengths and limitations of the study are discussed before presenting a final conclusion of the chapter.

1.6. Summary of chapter

This chapter provided an introduction to the study as well as a general overview of its main components. The definition of migraine was discussed, along with the influence of symptoms on every day functioning. A biopsychosocial lens was then used to discuss the potential relationships between migraine and both biological and psychological factors. In the rationale, it was argued that exploring the possible relationship between personality and migraine will contribute significantly to treatment approaches. The problem statement thereafter situates this study within its context. Summaries were provided on the aims, researcher questions, and hypotheses; and the research design. This study sought to investigate the relationship between the four temperament dimensions and serotonin with the expectation that the relationship with HA would be more significant. An additional aim of this study was to determine the temperament dimension distribution and serotonin concentration amongst MO sufferers. The expected finding was that the HA score would be increased in migraine patients as opposed to controls whilst serotonin concentration would be decreased. The dissertation structure was then presented before concluding.

CHAPTER 2: PERSONALITY, TRAIT, AND TEMPERAMENT

This chapter provides a brief historical overview of psychological approaches to personality, trait and temperament. This provides a historical backdrop of how conceptualizations of personality have changed over several decades in order to place the definitions used in this dissertation with the focus on Cloninger's Psychobiological Theory of Personality. It is beyond the scope of this dissertation to give full description of each theory in personality psychology, therefore only five major theories are discussed. These theories were selected due to the large impact they had, and continue to have, on shaping personality psychology. Thereafter, Cloninger's theory is discussed in detail including its developments, components, and critiques. Cloninger's theory is then used as a lens through which to explore the relationship between temperament and migraine.

2.1. Personality definition

The concept of "personality" generally incorporates the characteristic pattern of thoughts, feelings, and behaviours of an individual (Merikangas, Stevens, & Angst, 1993). Identifying and defining the core concepts of personality have been pursued since Hippocrates and Galen proposed the four humors in the second century (Clark, 2005; Dumont, 2010; Rettew & McKee, 2005; Stallings, Hewitt, Cloninger, Heath, & Eaves, 1996; Stelmack & Stalikas, 1991). However, the first academic personality theory is credited to Gordon Allport in 1937 (Corr & Matthews, 2009; Engler, 2009). Personality has since been viewed as a dynamic structure, which determines how an individual will react to his or her environment (Cloninger, Svrakic, & Svrakic, 1997; Rothbart, Ahadi, & Evans, 2000; Tuominen et al., 2013).

Personality psychology is focused on these relatively stable recurrent behaviours that differentiate individuals of the same age (Corr & Matthews, 2009). Several personality theories have been formulated since Allport and, although they are not all in agreement with the constructs forming personality, there seems to be consensus that both biological and psychological influences play a role (Engler, 2009; Tuominen *et al.*, 2013).

2.2. Temperaments and traits

Personality theorists often use terms such as trait, factor, dimension and disposition interchangeably (Strelau, 2001). In particular, trait and temperament have comparable definitions throughout literature. Montag (2014) defines a trait as the disposition an individual has for a specific type or degree of emotional reaction and as a stable quality that can be ascribed to an individual for a relatively long time period. Traits impact how a person thinks, behaves, and reacts emotionally to a variety of outside stimuli (McAdams & Pals, 2006; Montag, 2014). Temperament has been similarly defined as the individual differences in emotional reactivity which have an early appearance in life, are innate, and show relative stability (Rettew & McKee, 2005; Strelau, 2001; Watson, Gamez, & Simms, 2005; Wessman *et al.*, 2012).

Despite their current parallels, these concepts evolved over several decades of personality research. Delving into this history provides a better understanding of these terms, the methods used to study traits or temperaments, and how personality was or is perceived in either a trait- or temperament-oriented personality theory. The evolution of the constructs of trait and temperament is provided before comparing them and defining how they are used in this study.

Trait-oriented personality psychologists focused on structural analyses in order to build comprehensive taxonomies of descriptive traits (John, Robins, & Pervin, 2008; Nettle & Penke, 2010). In other words, personality psychology from a trait perspective suggests that an individual can be described in terms of certain characteristics which are relatively stable, enduring, and similar across different situations (Strelau, 2001; Yang et al., 2014). This dispositional approach to personality is one of the oldest and most persistent approaches (Engler, 2009).

The taxonomies in trait theories were constructed using the lexical hypothesis and psychometrics (Strelau, 2001). The lexical hypothesis assumes that individual differences are represented by the adjectives used in natural language and therefore analysis of the adjectives will render the individual traits (Ashton & Lee, 2005; De Fruyt, Van De Wiele, & Van Heeringen, 2000; Goldberg, 1993, 1999; John, Angleitner, & Ostendorf, 1988). In studies of personality, adopting the lexical approach would identify the terms in a language which are used to describe personality. This would render a representative sample of personality characteristics. Factor analysis would then be performed on these personality characteristics in order to obtain the major dimensions of personality variation (Ashton & Lee, 2005).

Although the lexical approach has been used widely in studies of personality, it received much criticism (Ashton & Lee, 2005): The lack of emphasis on the aetiology of the dimensions identified with this approach led to the critique that the trait personality theories could only describe behaviour rather than explain or predict it (Ashton & Lee, 2005; John et al., 2008; Nettle & Penke, 2010). Furthermore, due to the use of factor analysis, there was doubt that the resulting traits were 'real' entities rather than socially or cognitively constructed (Angleitner, 1991; Funder, 2009; John et al., 2008).

One of the most widely used personality theories, the five-factor model (FFM), was derived using the lexical and psychometric methods and there are still extensive debates regarding its five factors in the 'Big Five' (Block, 1995a, 1995b; Costa Jr & McCrae, 1995; Goldberg & Saucier, 1995; McCrae & Costa Jr, 1987). Block (1995a) offered several critiques of the FFM regarding its roots, the sole use of factor analysis to generate the theoretical constructs of personality, and the claims and implications of this approach (Block, 1995a). Replies to these criticisms were authored by Costa Jr and McCrae (1995) as well as Goldberg and Saucier (1995) to which Block (1995b) responded in a second article. In this reply, Block (1995b) refuted claims that he was calling for a complete halt of the FFM but rather seeking to incite further research by critiquing it before the theory was embraced. He concluded, rather fatalistically, that the theory either would or would not be adopted (Block, 1995b). Research into personality traits continued and Self-report agreement as well as stability over time provided support for the validity of personality traits (McCrae, 2002; Simms, Zelazny, Yam, & Gros, 2010).

There was doubt regarding consistency of traits across varied situations (Angleitner, 1991; Nezlek, 2007; Strelau, 2001) leading to the 'person-situation debate' (Fleeson & Nofle, 2009; Funder, 2006; Jackson, Hill, & Roberts, 2012; Nettle & Penke, 2010; Yang et al., 2014). As opposed to trait models, situationally focused theories involved "relatively specific relationships between relatively specific situational influences and relatively specific outcomes" (Nezlek, 2007, p. 790). Studies of the latter were mostly conducted in laboratories which gave the appearance of empirical support (Nezlek, 2007).

Ultimately, both situation and traits were incorporated and integrated models received increasing interest (Nezlek, 2007). Thus, after decades of research the existence of

personality traits as entities, rather than labels, their cross-temporal consistency, and their predictive ability were generally accepted (Funder, 2009; John et al., 2008; Strelau, 2001).

Temperament also has a long history, dating back to Greek philosopher-physicians Hippocrates and Galen in the fifth century B.C. (Buss, 1990; Clark, 2005; John et al., 2008; Zuckerman, 1995). Temperament was believed to reflect the blend of four bodily fluids or humors within the individual (John et al., 2008; Mathewson, Miskovic, & Schmidt, 2012; Zuckerman, 1995). A later extension of this theory stated that a predominance of one humor would indicate a temperament type: Sanguine (blood), choleric (bile), phlegmatic (phlegm), or melancholic (black bile) (Clark, 2005; John et al., 2008; Mathewson et al., 2012). Although no longer the dominant view, two features of this theory endure in current theories of temperament. The first is that there is a biological basis to observable characteristics (John et al., 2008; Strelau, 1987; Watson et al., 2005). The second feature is that emotions - both their experience and regulation - are essential and defining aspects of temperament (John et al., 2008; Watson et al., 2005). A number of personality theories that developed from a temperament perspective, including Cloninger's theory which is the theory of focus for this dissertation, possess these two key elements. However, the trait and temperament construct definitions have become increasingly similar and the inclusion of these features is no longer the defining characteristic of temperament-based personality theories.

John et al. (2008) report the convergence of the trait and temperament approaches to personality as following three phases: 1) Research indicating a genetic component of personality traits, 2) Association between traits and differences in emotional reactivity, and 3) An eventual consensus on the number of personality traits allowing for narrower focus as well as more complex theory and hypotheses leading to clarification of their real-world

correlates (Angleitner, 1991; Buss, 1990; John et al., 2008). This makes the current similarity between the definitions for trait and temperament understandable. However indecision remains regarding whether temperament is subsumed by trait or *vice versa*. John et al. (2008) reported that the above three developments led to traits being viewed as psychobiological dimensions of temperament. In this vein, McCrae et al. (2000) noted that the traits in the Big Five theory and temperament could both be defined as biologically-based dispositions that are intrinsically determined and largely independent of environment. He states therefore that the five traits would be subsumed by temperament (McCrae et al., 2000). However, another way to view the relationship between trait and temperament is to follow the argument laid out by Strelau (2001). Trait-oriented personality theories use the individual differences approach. Therefore, a trait is the basic unit used to describe individual differences. Studies into temperament also use the individual differences approach, describing temperament in trait units (Strelau, 2001). Thus, temperament is a part of personality under the trait-oriented personality structure (Endler, 1989; Strelau, 1987, 2001) and it is impossible to separate temperament research from the concept of trait (Strelau, 1987, 2001).

In conclusion, trait and temperament currently have several common elements. However, the differing histories should be kept in mind during discussion of each personality theory as they have implications for how the theory was developed and its basic assumptions. Strelau (2001) identifies three further points to take into account. Firstly, it is the *tendency* to behave and react in a specific way which can be regarded as existing in reality. Traits or temperaments cannot be reduced to the behaviours, reactions, and physiological mechanisms themselves. Therefore, and secondly, direct testing is not possible. Instead, tendencies are indirectly measured through assessment of the behaviours and reactions that express the tendency. Lastly, personality consists of both temperamental and non-temperamental traits.

The latter are often referred to as character (Strelau, 2001). Taking note of the above, in this dissertation the terms “temperament” and “trait” are used to refer to the biological, innate tendency to behave in a certain manner as indicated by measurable behaviours. Non-temperamental traits are referred to as “character traits”.

In the next section (Section 2.3) selected personality theories from either the biological (temperament) perspective or the trait perspective are discussed. This provides a brief history of personality theories influential in the development of the Psychobiological Theory of Personality.

2.3. Personality theories

Although there are different approaches, it should be noted that these perspectives have developed over time and have on occasion impacted each other (Corr & Matthews, 2009). Corr and Matthews (2009) identify six major perspectives of personality: biological, cognitive, humanistic, learning, psychodynamic, and trait. Each perspective differs in the methods used to create an overall theory of personality, in what observations can be made by the researchers and in what interventions can then be applied by practitioners (Corr & Matthews, 2009). In this structure, theories referring to temperament would be categorized into the biological perspective (Corr & Matthews, 2009; McCrae et al., 2000) and trait theorists into the trait perspective (Corr & Matthews, 2009). It is beyond the scope of this chapter to discuss each personality theory and instead several theories in the biological and trait perspectives have been selected for discussion: the Three-Factor Theory, the Five-Factor Theory, the Alternative Five-Factor Theory, the Reinforcement-Sensitivity Theory, and the

Psychobiological Theory of Personality. These have been, highly influential theories in the history of personality psychology.

Since these theories were developed over several decades, a timeline is provided to aid the reading of this section. Figure 2.1 depicts important dates and publications within the period 1920 to 2000 with regards to the five chosen theories.

2.3.1. The Three-Factor Theory

Hans Jürgen Eysenck is considered the “father of the biological approach to personality” (Zuckerman, 2004, p. 17). He developed a three-factor model to describe personality. The three factors are Extraversion-Introversion, Neuroticism-Stability, and Psychoticism-Superego Function (PEN) (Corr & Matthews, 2009; Eysenck, 1990; Feist & Feist, 2008; Giancola, Zeichner, NewBolt, & Stennett, 1994; Zelenski & Larsen, 1999; Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993). These three factors are considered bipolar. For example, Extraversion would be at one pole and Introversion at the other. However, this is not to say that a typical individual is at one or the other pole of a factor (Feist & Feist, 2008). Rather, these factors are dimensional and a typical individual could be placed at any point on the continuum. Eysenck proposed that most individuals would fall within the average range of each factor, with the exception of Psychoticism which is skewed towards low scores, giving a unimodal, normal distribution rather than bimodal distribution of scores within the population (Eysenck, 1970, 1992; Feist & Feist, 2008; Matthews, Deary, & Whiteman, 2010).

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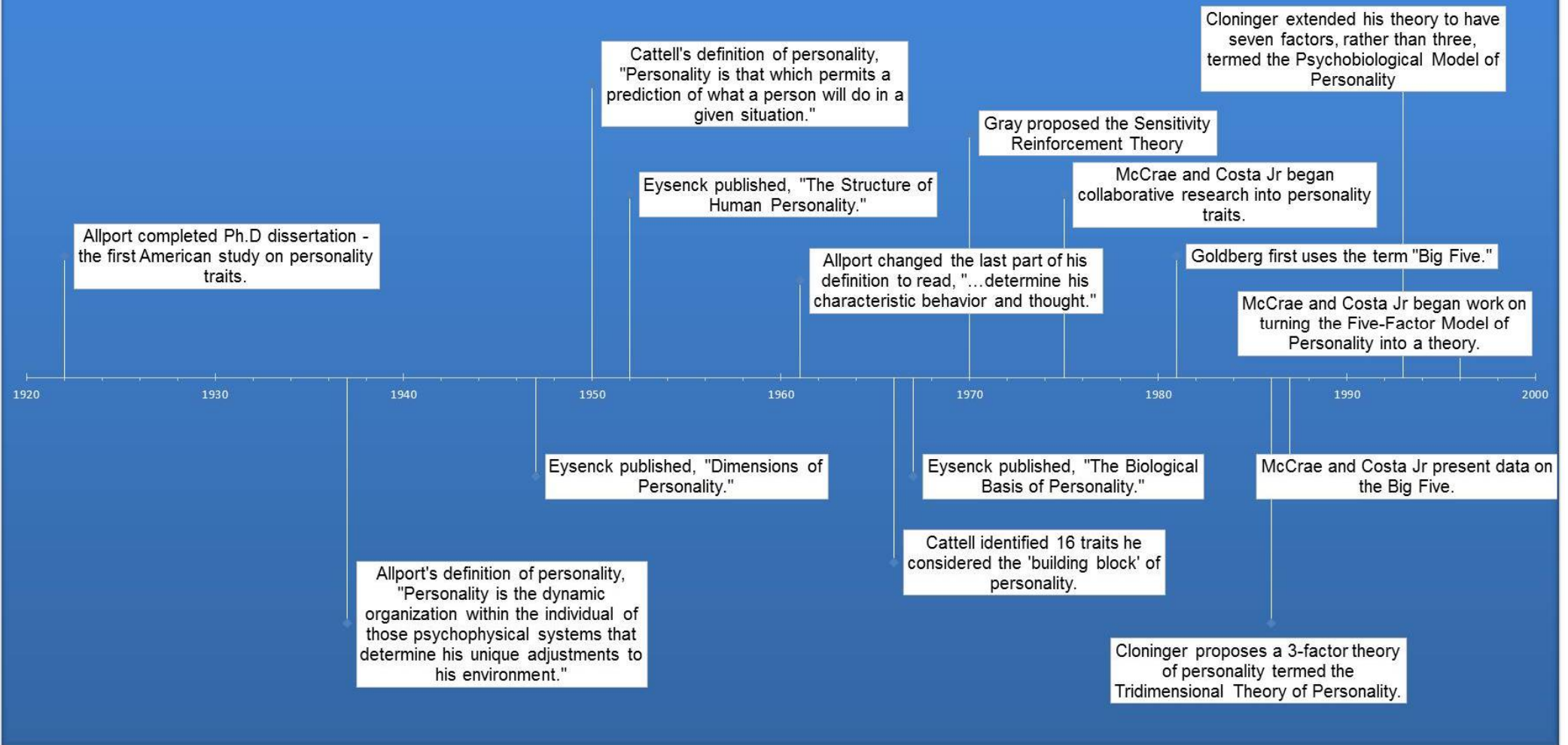


Figure 2.1. Personality theory timeline indicating first proposal dates and significant revision dates.

These three traits are based on biological mechanisms (Eysenck, 1990). The reticulo-cortical and reticulo-limbic circuits of the brain's ascending reticular activating system (RAS) play key roles in this theory (Corr & Matthews, 2009; Matthews & Gilliland, 1999). The reticulo-cortical circuit commands cortical arousal to stimuli, the Extraversion-Introversion dimension (Matthews & Gilliland, 1999). It is proposed that extraverts have a higher cortical arousal threshold as well as a higher arousal tolerance level (Gao et al., 2013). The reticulo-limbic circuits controls response to emotional stimuli, the Neuroticism-Stability dimension (Matthews & Gilliland, 1999). Individuals who score high on the Neuroticism pole have low thresholds, as well as higher activation levels, within the subcortical structures of the limbic system (Gao et al., 2013). When the emotional stimuli are strong enough, the resultant activity of the limbic system may spread to the cortex (Matthews & Gilliland, 1999). The Eysenck Personality Inventory (EPI) or the Eysenck Personality Questionnaire (EPQ) are used to assess these traits (Carver & Miller, 2006; Eysenck, 1990).

2.3.2. The Reinforcement Sensitivity Theory

Jeffrey A. Gray was Eysenck's student and based his work on that of his predecessor. Gray focused on the neurobiological determinants of personality. He began to develop the 'conceptual nervous system' consisting of three functional systems that could be related to specific brain structures or systems (Beauchaine, 2001; Corr & Matthews, 2009; Mitchell et al., 2007). These three systems are the Behavioural Approach System (BAS), the Behavioural Inhibition System (BIS), and the Fight-Flight-Freezing System (FFFS).

The BAS regulates sensitivity to reward and its activation permits or increases behaviour, moving the individual towards their objectives (Beauchaine, Gatzke-Kopp, &

Mead, 2007; Mitchell et al., 2007; Monteleone, Scognamiglio, Monteleone, Perillo, & Maj, 2014). In earlier versions of his theory, Gray proposed that this system responded to conditioned signals of reward but this was later extended to include unconditioned signals (Smillie, Pickering, & Jackson, 2006). This system is associated with the mesolimbic dopaminergic pathways ascending from the brain stem (Beauchaine et al., 2007; Beauchaine, 2001; Matthews & Gilliland, 1999; Smillie, 2008). The perfusion of dopamine following a stimulus is posited to result in the rewarding effect (Beauchaine et al., 2007; Nader, Bechara, & van der Kooy, 1997). Elation and relief are posited to be the emotions associated with this system (Mitchell et al., 2007; Poropat & Corr, 2015).

The second system, the BIS, was proposed to be involved in regulating sensitivity to conditioned signals of punishment (Monteleone et al., 2014; Smillie et al., 2006) and conditioned signals of non-reward (Smillie et al., 2006). The BIS included the amygdala (Mitchell et al., 2007; Smillie, 2008), periaqueductal grey, medial hypothalamus, posterior cingulate, and prefrontal dorsal stream (Mitchell et al., 2007). It was proposed that the BIS system was mediated by serotonergic projections, from the raphe nucleus, and noradrenergic projections, from the locus ceruleus (Beauchaine, 2001; Smillie, 2008). A septo-hippocampal comparator was suggested to detect mismatch between predicted and actual events (Cloninger, 1987; Matthews & Gilliland, 1999). Cognitive control over anxiety and signals from primitive brain areas was deemed possible in this model as the comparator works in concert with other brain structures, such as the prefrontal cortex (Matthews & Gilliland, 1999). However, the revised theory postulates that this system responds to and resolves conflict between the BAS and the FFFS systems, with a bias towards the FFFS (Mitchell et al., 2007; Smillie et al., 2006). Activation of this system prompts cautionary or risk assessment behaviour and increases both arousal and attention (Matthews & Gilliland, 1999;

Mitchell et al., 2007; Smits & Boeck, 2006). Therefore, this system is related to anxiety (Mitchell et al., 2007; Poropat & Corr, 2015; Smits & Boeck, 2006).

As opposed to the BIS response to conditioned stimuli, the Fight-Flight System (FFS) was initially theorized to respond only to negative stimuli with immediate repercussions and that are unconditioned, causing an immediate active avoidance or attempted eradication (Beauchaine, 2001; Corr & Matthews, 2009; Smillie et al., 2006; Smits & Boeck, 2006). The FFFS, including a “freezing” component, is now proposed to respond to all negative signals, both conditioned and unconditioned, and therefore subsumes the original role of the BIS. The FFFS is biologically linked to the amygdala, hypothalamus, periaqueductal grey (Beauchaine, 2001; Corr & Matthews, 2009; Mitchell et al., 2007; Smillie, 2008), anterior cingulate cortex (Mitchell et al., 2007; Smillie, 2008), and prefrontal ventral stream (Mitchell et al., 2007). It is associated with the emotions of panic (Mitchell et al., 2007; Smits & Boeck, 2006), fear (Mitchell et al., 2007; Poropat & Corr, 2015; Smillie, 2008; Smits & Boeck, 2006), and rage (Beauchaine, 2001).

The Reinforcement Sensitivity Theory (RST) was initially proposed in 1970 but was further developed and refined over several decades (Corr & Matthews, 2009; Mitchell et al., 2007). This theory proposes that personality traits are determined by the sensitivity of each of the three brain systems (Corr & Matthews, 2009; Monteleone et al., 2014). When one considers the reflection of these systems in personality, high BIS sensitivity was categorized by Gray as Anxiety whilst high BAS sensitivity was categorized as Impulsivity (Mitchell et al., 2007; Smillie et al., 2006; Zelenski & Larsen, 1999). These two dimensions are typically considered to be 45° rotations of Eysenck’s Neuroticism and Extraversion (Mitchell et al., 2007; Zelenski & Larsen, 1999), although the correct angle is closer to 30° (Corr &

Matthews, 2009; Mitchell et al., 2007; Smillie et al., 2006). That is, Anxiety was considered a combination of Introversion and Neuroticism, 30° rotation closer to Neuroticism, whilst Impulsivity combined Extraversion and Neuroticism, 30° rotation closer to Extraversion (Mitchell et al., 2007; Zelenski & Larsen, 1999). Figure 2.2 is a graphic indication of Gray's modification of Eysenck's original dimensions. Carver and White developed the BIS/BAS scales as a means of assessing the personality dimensions generated by this theory (Mardaga & Hansenne, 2007).

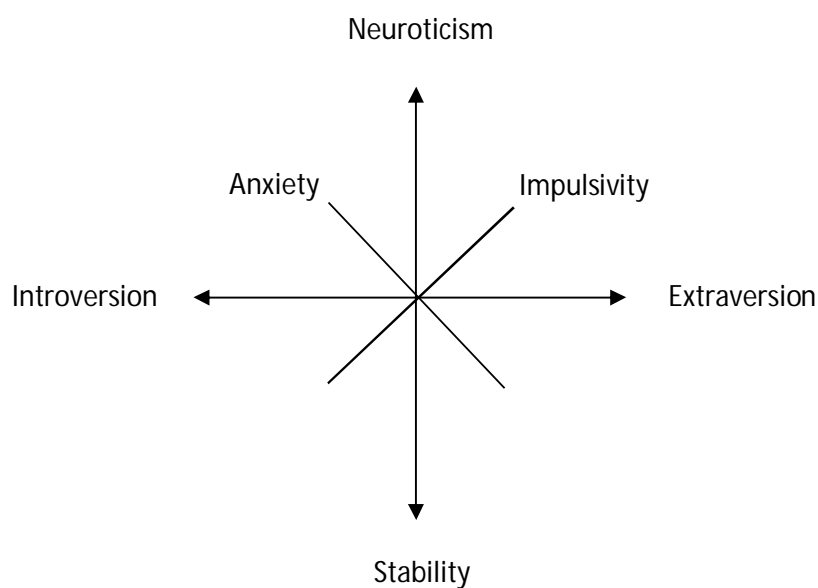


Figure 2.2. Gray's personality dimensions in relation to Eysenck's dimensions (Adapted from Corr and Matthews, 2009).

Gray's theory underwent further revision: Individuals that are high on the Impulsivity axis were postulated to be more sensitive to signals of reward compared to those who measured low on this axis. Therefore, this axis was renamed "Reward Sensitivity" and reflects Impulsivity and BAS activity. Persons high on the Anxiety axis were proposed to have a greater sensitivity to signals of punishment. Thus, this axis was termed "Punishment Sensitivity" to reflect Anxiety as well as BIS and FFFS activity (Corr & Matthews, 2009; Mitchell et al., 2007). The structures and processes involved when an individual responds to

punishment or reward as explained by RST are depicted in Figure 2.3 (Adapted from Smillie, 2008). When either the BAS or the FFFS is activated, by reward or punishment respectively, the other system is inhibited. When both are activated, the BIS is also activated in order to resolve the approach-avoidance conflict, favoured towards the FFFS. As stated above, BAS activity is representative of Reward Sensitivity whilst both BIS and FFFS functioning determine Punishment Sensitivity. These changes to the Gray's theory are represented in Figure 2.3.

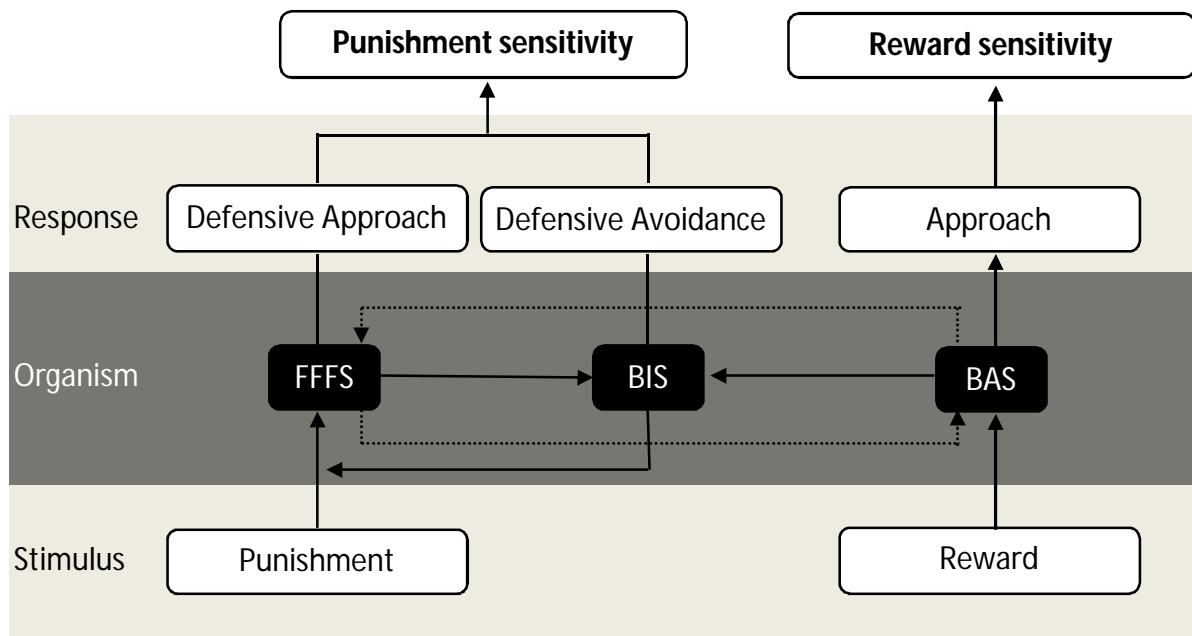


Figure 2.3. Structures and processes involved in reinforcement sensitivity as understood in the RST (Adapted from Smillie, 2008).

This revision allowed for an explanation of differences in cortical arousal between introverted and extroverted individuals. Introverted individuals are considered to have higher cortical arousal than their extroverted counterparts. This is in line with their proposed higher sensitivity to punishment (punishment is more arousing than reward) (Corr & Matthews, 2009).

2.3.3. The Five-Factor Theory of Personality

Initial investigation into the Five-Factor Theory of Personality involved language and consisted of analysing the words used to describe human characteristics (Montag, 2014; Stallings et al., 1996). This is based on the lexical hypothesis, which assumes that differences between individuals are encoded in natural language. More specifically, these differences are represented by the adjectives used to describe traits (De Fruyt et al., 2000; Goldberg, 1993; John et al., 1988).

The work of several researchers was influential in the development of the Five-Factor Theory of Personality. Some of the first researchers included Gordon Allport and Raymond Cattell (Feist & Feist, 2008). Allport and Odbert (1936) constructed a taxonomy of 17,943 terms used to describe personality, divided into four alphabetical lists. The first listed those identified as stable traits, approximately 4,500 terms (Goldberg, 1990). Cattell (1943, as cited in Goldberg, 1990) began his investigation with the latter list and a variety of sources to create 171, mostly bipolar, scales (Engler, 2009; Goldberg, 1990). Correlations between scales guided Cattell (1943, as cited in Goldberg, 1990) to the development of a set of 35 bipolar clusters of related terms which he then used to inform rating scales. He assessed 13 groups of 16 male participants each ($N = 208$) and the correlations between the variables were factored (Cattell, 1945; Goldberg, 1990). Using this method, he ultimately identified sixteen traits of personality which are assessed by the Sixteen Personality Factor Questionnaire (16PF) (Engler, 2009). Robert R. McCrae and Paul T. Costa, Jr, are two researchers who played significant roles in the development of this theory. McCrae was highly interested in the psychometric work of Cattell and he investigated personality traits during his graduate studies. During the 1970s, McCrae and Costa Jr conducted work together

on analysing traits using factor analytic techniques. They initially focused on Neuroticism and Extraversion, but fairly quickly also discovered a third factor they termed Openness to Experience.

This approach generated the five personality dimensions: Openness to experience, Conscientiousness, Agreeableness, Extraversion, and Neuroticism. Extraversion and Neuroticism in particular have been used to emphasize the link between personality and emotional tendencies (Montag, 2014). Factor analysis of personality questionnaires and ratings consistently identified these five major traits, resulting in the Five-Factor Model (FFM) (Engler, 2009; Mitchell et al., 2007). The term “Big Five” was first used by Lewis Goldberg in 1981 following multiple factor analyses of personality traits by several research teams (Feist & Feist, 2008). Following additional development and refining by McCrae and Costa Jr, this model became a theory (Feist & Feist, 2008). Thus several researchers contributed in the development from taxonomy to model to theory. The research by McCrae and Costa Jr also led to the most commonly used test to assess these dimensions: the Revised NEO Personality Inventory (NEO-PI-R) (Carver & Miller, 2006; Mitchell et al., 2007).

2.3.4. The Alternative Five-Factor Model

Marvin Zuckerman focused on the psychobiological aspect of personality. In this theory it is hypothesized that personality is reflected by five factors and differences in each factor are influenced by neurotransmitters, enzymes, and gonadal hormones (García, Escorial, García, Blanch, & Aluja, 2012). The five factors were revealed following multiple factor analyses and include: Sociability, Neuroticism-Anxiety, Impulsive Sensation-Seeking, Aggression-Hostility, and Activity (Zuckerman, 2004). This model was called the Alternative

Five-factor Model (Carver & Miller, 2006; Zuckerman, 2004). The Zuckerman-Kuhlman Personality Questionnaire (ZKPQ) was developed to assess these personality factors (Carver & Miller, 2006; Zuckerman, 2004).

2.3.5. The Psychobiological Theory of Personality

C. Robert Cloninger also proposed a psychobiological personality model (Cloninger, Svrakic, & Przybeck, 1993; Cloninger, 1987). In their theories, both Cloninger and Zuckerman incorporated and built on a biochemical basis for individual differences by relating these differences to neurotransmitter system activity (Mathewson et al., 2012). Cloninger's theory is one of the most commonly used theories in studies of personality (Margetić & Jakovljević, 2013; Miettunen et al., 2004). According to this theory, personality is the organization of psychobiological systems which modulate how an individual learns from experience and consequently adapt their thoughts, feelings, and behaviours (Cloninger et al., 1997; Constantino, Cloninger, Clarke, Hashemi, & Przybeck, 2002; Mochcovitch et al., 2012; Svrakic, Svrakic, & Cloninger, 1996).

There are two main interrelated domains in this theory: Temperament and character. Temperament refers to automatic, emotional responses associated with procedural learning and memory as well as neurobiological predispositions, with genes playing a role from an early age (Cloninger et al., 1997; Gruzca, 2003; Mochcovitch et al., 2012; Svrakic et al., 1996). Character is representative of more complex cognitive processes based on propositional learning and memory (Cassimjee & Murphy, 2010; Mochcovitch et al., 2012; Svrakic et al., 1996). That is, character traits are proposed to represent the influence of social and environmental factors in adolescence and adulthood (Constantino et al., 2002; Josefsson

et al., 2013; Peirson et al., 1999; Svrakic et al., 1996). A non-linear dynamic system results from the interaction of these two domains. This system regulates the development of personality as the individual ages (Figure 2.4) (Josefsson et al., 2013).

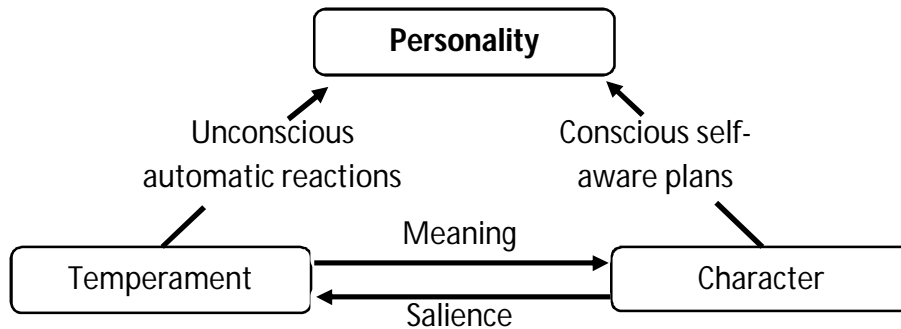


Figure 2.4. Structure of personality, temperament, and character in Cloninger's theory (Adapted from Cloninger, 1994)

This theory was developed over several decades. In the late 1980s, Cloninger initially proposed a three-factor theory to describe the structure of personality (Gillespie, Cloninger, Heath, & Martin, 2003; Heath, Cloninger, & Martin, 1994; Mochcovitch et al., 2012; Stallings et al., 1996; Verweij et al., 2010; Zuckerman, 1995) termed the Tridimensional Theory of Personality (Harro et al., 2009). It is measured by the Tridimensional Personality Questionnaire (TPQ) (Bond, 2001). This theory was subsequently revised and the three original temperament dimensions, Novelty Seeking (NS), Harm Avoidance (HA), and Reward Dependence (RD), were joined by a third, Persistence (P). This dimension had originally been viewed as part of RD but emerged as an independent dimension following multiple factor analysis studies (Gillespie et al., 2003; Mochcovitch et al., 2012; Stallings et al., 1996; Verweij et al., 2010; Zuckerman, 1995).

NS is related to the level of activation of exploratory activity, while HA indicates the efficiency of behavioural inhibition (Bond, 2001; Cassimjee & Murphy, 2010; Celikel et al.,

2009; Cloninger et al., 1993; Grucza, 2003; Klein et al., 2011; Mochcovitch et al., 2012). The latter is the tendency to inhibit response when aversive stimuli are presented in order to avoid punishment and behaviour which is not rewarded (Strakowski, Stoll, Tohen, Faedda, & Goodwin, 1993). RD is related to the maintenance of rewarded behaviour, whereas P indicates maintenance of behaviour in spite of frustration and fatigue (Bond, 2001; Cassimjee & Murphy, 2010; Celikel et al., 2009; Cloninger et al., 1993, 2012; Grucza, 2003; Klein et al., 2011; Mochcovitch et al., 2012).

Self-directedness (SD), Cooperativeness (CO), and Self-transcendence (ST) were also included in the model as character traits (Mochcovitch et al., 2012; Verweij et al., 2010; Zuckerman, 1995). These character traits were incorporated so as to account for the effects of social learning, culture, and environment and arise from differences in higher cognitive functions, as opposed to the more genetically determined and emotional temperament dimensions (Celikel et al., 2009; Cloninger et al., 1998). Temperament restricts but does not determine character development. The latter is the result of events, social learning and experiences, which are interactions of systems. Therefore, the end result cannot be predicted based on simple event summation (Cloninger et al., 1997; Farmer & Goldberg, 2008a).

The Temperament and Character Inventory (TCI) was developed to assess all seven personality dimensions (Bond, 2001). Descriptors of low or high scores in the temperament dimensions are presented in Table 2.1 (Cloninger et al., 1997; Farmer & Goldberg, 2008a; Svrakic et al., 1996). The first column states the temperament or character dimension. The adjacent two columns list adjectives which could be applied to a typical individual scoring - either low or high - in that dimension.

Table 2.1

Low and high temperament and character dimension descriptors

Personality dimension	Descriptors of persons low and high on temperament and character dimensions	
	<u>Low</u>	<u>High</u>
Temperament dimension		
Novelty Seeking (NS)	Reserved; Rigid; Thrifty; Stoical	Exploratory; Impulsive; Extravagant; Irritable
Harm Avoidance (HA)	Optimistic; Daring; Outgoing; Vigorous	Pessimistic; Fearful; Shy; Fatigable
Reward Dependence (RD)	Detached; Aloof; Critical; Independent	Sentimental; Open; Warm; Sympathetic
Persistence (P)	Apathetic; Spoiled; Underachiever; Pragmatist	Industrious; Determined; Ambitious; Perfectionistic
Character dimension		
Self-directedness (SD)	Blaming; Aimless; Inept; Vain	Responsible; Purposeful; Resourceful; Self-accepted
Cooperativeness (CO)	Prejudiced; Insensitive; Hostile; Revengeful	Reasonable; Empathic; Helpful; Compassionate
Self-transcendent (ST)	Undiscerning; Empirical; Unimaginative; Dualistic; Practical	Judicious; Intuitive; Inventive; Transpersonal; Spiritual

In 2004, the theory was further revised in order to include empirical findings and the most recent studies. In this model, the temperament and character dimensions were retained, but personality was regarded as a three-dimensional spiral structure with five different layers. These layers are referred to as “planes of being” (Mochcovitch et al., 2012, p. 344) and include sexuality, materiality, emotionality, intellectuality, and spirituality (Cloninger, 2008, 2009; Mochcovitch et al., 2012). Each plane modulates a basic emotional conflict. The ability to modulate these conflicts is the result of maturation (Cloninger, 2004), which stems from the evolution of the brain systems in a series of steps over time. This evolution makes it possible for an individual to adopt the different perspectives of each plane (Cloninger, 2008), thus allowing “survival of progressively more flexible, aware, and creative organisms” (Cloninger, 2008).

It was proposed that conscious thought is concerned with the regulation of the five planes of being (Cloninger, 2004, 2009). Furthermore, interactions among the five planes creates a 5×5 matrix of 25 sub-planes which regulate the basic drives (Cloninger, 2008, 2009). This means that, while viewing a situation from a specific plane, e.g. sexual, individuals can still have an even more specific focus, e.g. the material objective of reproduction (Cloninger, 2008). Each sub-plane relates to a temperament dimension subdimension or basic emotion, as depicted in Table 2.2 (Cloninger, 2004, 2008, 2009; Mochcovitch et al., 2012). The temperament subdimension renders a quantitative measure of the emotional conflict within each of the sub-planes (Cloninger, 2004). The final result is a 5×5×5 matrix which incorporates both conscious and subconscious thoughts (Cloninger, 2009).

Table 2.2

5×5 Matrix where each sub-plane corresponds to a temperament subdimension

Sub-plane	Sexual plane	Material plane	Emotional plane	Intellectual plane	Spiritual plane
Spiritual plane	Shy vs beguiling (HA3)	Exploratory vs unexcitable (NS1)	Attached vs detached (RD3)	Perfectionist vs pragmatic (P4)	Peaceful
Intellectual plane	Pessimistic vs optimistic (HA1)	Impulsive vs rigid (NS2)	Sentimental vs indifferent (RD1)	Determined vs ambivalent (P2)	Patient
Emotional plane	Inhibited vs uninhibited (HA total)	Irritable vs stoic (NS total)	Sociable vs distant (RD total)	Persistent vs impersistent (P total)	Charitable
Material plane	Fearful vs risk-taking (HA2)	Extravagant vs frugal (NS3)	Warm vs aloof (RD2)	Eager effort vs lazy (P1)	Respectful
Sexual plane	Fatigable vs vigorous (HA4)	Disorderly vs regimented (NS4)	Dependent vs independent (RD4)	Ambitious vs underachieving (P3)	Hopeful

NS=Novelty Seeking; HA=Harm Avoidance; RD=Reward Dependence; P=Persistence (Adapted from Cloninger, 2008; Mochcovitch et al., 2012)

This theory was originally based on an attempt to integrate the neurotransmitter systems and personality into a unified model (Margetić & Jakovljević, 2013). Therefore, an important facet of this theory is that the temperaments are assumed to be underpinned by different neurotransmitter systems. NS is linked with dopamine, HA with serotonin, RD associated with epinephrine, and P is related to glutamate (Abbate-Daga et al., 2007; Montag, 2014). The empirical support for this theory has been divided, but it is still regarded as a valuable theory in personality research (Montag, 2014).

2.3.5.1. Singularity of the Psychobiological Theory of Personality

According to Gillespie et al. (2003), Cloninger's theory differs from other personality theories in two ways. Firstly, the concepts and their interactions to create personality variation are theorized differently (Gillespie et al., 2003) to many other theories. However, there is some overlap of terms or their meanings with other personality theories, which are presented in Table 2.3 (Brändström, 2009; Cloninger, 2008; Mardaga & Hansenne, 2007; Rettew & McKee, 2005; Smillie et al., 2006; Smillie, 2008). HA overlaps with terms relating to neuroticism introversion, or inhibition. It is therefore also seen as negatively correlating with extraversion and appetitive behaviour, which overlaps with NS. RD often corresponds to extraversion, openness and agreeableness from the Five-Factor Theory of Personality whilst P overlaps with conscientiousness from same. Secondly, the influences of biology and genetics as well, as social environment and learning are afforded equal weight in the determination of an individual's personality (Gillespie et al., 2003). The latter is an important feature which is hereunder discussed further.

Table 2.3.

Comparison between Cloninger's Psychobiological Theory of Personality and other personality theories

Approach to personality:	HA	NS	RD	P	SD	CO	ST
Cloninger							
Eysenck	Neurotic introvert	Neurotic extrovert Psychoticism	-Psychoticism		-Neuroticism	-Psychoticism	
Gray	BIS, Anxiety -BAS	BAS, Impulsiveness					
FFM and correlations with NEO-PI-R	Neuroticism -Extraversion	Extraversion - Conscientiousness	Extraversion, Openness, Agreeableness	Conscientiousness	Conscientiousness Extraversion -Neuroticism	Agreeableness	Openness Extraversion
Zuckerman	Neuroticism- Anxiety	Impulsive Sensation-seeking		Activity		-Aggression- Hostility	

HA=Harm Avoidance; NS=Novelty Seeking, RD=Reward Dependence; P=Persistence; SD=Self-Directedness; CO=Cooperativeness; ST=Self-Transcendence; BIS=Behavioral Inhibition System; BAS=Behavioural Activation System; FFM=Five Factor Model (NEO-PI-R)
 - Indicates a negative correlation with Cloninger's dimensions

Gillespie et al. (2003) noted that the separation of temperament and character has long been a feature of personality psychology. Indeed, this can be seen in the previously discussed theories where biological and psychological features are included but divided. What remains unique to the Psychobiological Theory of Personality is that genetics contribute to both temperament and character dimensions and it is rather **learning** which differentiates them from each other. Whilst other theories have similar mechanisms contributing to personality, such as the Alternative Five-Factor Theory which also includes biological factors such as neurotransmitters as well as five psychological factors, Cloninger's theory makes allowance for an iterative process where personality is developed through learning both unconsciously, using behavioural (procedural) conditioning, and consciously, using higher cognitive processes (propositional). This further links to how the theory was developed.

It was argued by Cloninger that models of personality are required to differentiate between perceptual and conceptual aspects of memory in order to avoid failure (Gillespie et al., 2003). Therefore, the development of the Psychobiological Theory of Personality was based on within-subject variation with regards to learning as opposed to between-subject variation in behaviour (Gardini, Cloninger, & Venneri, 2009). Within-subject differences refer to the variation on a variable for one individual over time. Between-subject variation measures the difference between individuals on a variable (Mroczek, Spiro, & Almeida, 2003). Therefore, the individual may change on a variable over time. This is an important point for migraineurs which is further discussed below under "Harm Avoidance, pain, and psychopathology" (section 2.7).

As a final point, it was also put forth that personality models should take into account underlying biological and social influences, not basing the model on factor analysis of

behaviour alone (Gillespie et al., 2003). Gardini et al. (2009) stated that a test derived from factor analysis assumes linear relationships between variables. However, this is unlikely to be the case when examining brain systems and therefore factor analysis alone is insufficient.

2.3.5.2. Criticisms of the Psychobiological Theory of Personality

Although Cloninger's model has been widely used in personality studies, some studies have identified specific oversights or contradictions. It is not clear whether failures to support the central tenets of the theory are due to limitations of the theory, limitations of the measures used to assess the theory, or both (Farmer & Goldberg, 2008a).

As mentioned previously, it is proposed in this theory that temperament influences the subsequent development of character (Cloninger et al., 1997; Farmer & Goldberg, 2008a). However, Farmer and Goldberg (2008a) report that the precedence of temperament was contradicted in the study by Constantino et al. (2002), who investigated the seven-factor model in early childhood by retesting pre-school children at 30 ($N = 40$) and at 65 ($N = 29$) months of age. Both temperament and character dimensions were approximately equally stable. Furthermore, there was no significant correlation between character dimension scores and age (Constantino et al., 2002; Farmer & Goldberg, 2008a). Age therefore did not influence character stability, indicating a role for genetic factors and/or processes based on experience occurring before two years of age, such as attachment (Constantino et al., 2002). This indicates that character would be influenced by both genetic factors and environment.

It should be noted that there is a discrepancy with regards to when the likelihood of the role heritability plays in character was acknowledged. In their article introducing the

character dimensions, and thereby introducing the seven-factor model, Cloninger et al (1993) stated that it “is likely that genetic factors are as important in character development as they are for temperament” (Cloninger et al., 1993, p. 988). It was proposed that the heritability of character traits may explain why, in two individuals of similar temperament, one continues to behave in maladaptive patterns and the other does not (Cloninger et al., 1993). However, in later articles it is reported that Cloninger initially assumed that character was weakly heritable (Corr & Matthews, 2009; Farmer & Goldberg, 2008b; Gillespie et al., 2003) and Cloninger (2008) himself acknowledged that earlier versions of his theory expected that character development reflected learned higher cognitive processes, limiting heritability. Notwithstanding, character heritability was confirmed and it was also noted that there are substantial genetic influences on character dimensions (Ando et al., 2004; Cloninger, 2008; Gillespie et al., 2003; Josefsson et al., 2013).

Genetic aetiology is therefore not the distinguishing factor between character and temperament (Ando et al., 2004; Farmer & Goldberg, 2008a; Josefsson et al., 2013). Rather, the former is a concept-based process whilst the latter refers to inter-individual differences in perceptual processing and habit formation (Cloninger et al., 1993; Korner, Gerull, Stevenson, & Mearns, 2007). All individuals perceive the environment and react to it. Initially temperament, as innate and biological, shapes perceptions and reactions. Perceptions are then cognitively organized into abstract symbols and self-concepts are developed. Self-concepts determine stimuli significance and salience. This modifies our unconscious and automatic reactions. In this epigenetic iterative process both temperament and character development interact with each other and motivate behaviour (Cloninger et al., 1993).

However, culture and social learning are important factors in self-concept development. Therefore it is suggested that the environment would be of more importance for character development than for temperament (Cloninger et al., 1993). Therefore, a genetic basis for character strengthens the seven-factor model as it shows that each dimension should be included (Gillespie et al., 2003) and heritability of both domains does not detract from the socio-cultural influences on character development.

The heritability and correlation between the temperament and character domains also led to the criticism that they are not qualitatively different personality domains. Josefsson et al. (2013) investigated the hypothesis that the effect size of change over the lifespan would be larger for character dimensions than for the temperament dimensions. In this study 3 596 Finnish participants, consisting of six birth cohorts, were followed for 27 years. The sample was aged 3 to 18 at the baseline phase in 1980. There were eight follow-up phases during the period 1980 to 2007. Change effect sizes were large for all three character dimensions while for temperament dimensions the effects sizes were moderate for NS (-), weak for both P (+) and RD (-), and almost zero for HA. These results indicated qualitative differences regarding the developmental patterns of temperament and character, as opposed to their moderate cross-sectional correlations. Also, birth year had an influence on the developmental pathway of character dimensions only. Therefore, temperament and character should be considered separate domains in order to gain this qualitative information (Josefsson et al., 2013).

A further dispute is that the proposed relationships between each temperament dimension and a single neurotransmitter system have not been conclusively delineated (Farmer & Goldberg, 2008a, 2008b; Paris, 2005). Cloninger (2008) responded that lack of consideration of temperament, neurotransmitter system, and location and connections

amongst brain areas will usually indicate weak or inconsistent associations between these three factors. In reply, Farmer & Goldberg (2008b) noted that Cloninger did not outline these considerations and nor did he provide predications regarding the outcome if these considerations were met. Failure to provide this information prevents precise hypothesis formulation and therefore the theory itself allegedly cannot be falsified empirically (Farmer & Goldberg, 2008b).

The contradictory findings regarding these relationships between temperaments and neurotransmitter systems also cause doubt as to whether temperament profiles could provide information about the efficacy of a given pharmacological intervention (Farmer & Goldberg, 2008a). Although the current study does make reference to the hypothesis that understanding the temperament profile of an individual could aid in their treatment plan, this study does not investigate the relationships between temperament, mood and psychiatric disorders, and pharmacological interventions. This could be examined in future studies. Therefore, this criticism serves to indicate that there have been contradictory findings reported and this will be kept in mind when reviewing the findings of this study.

Despite these arguments, the Psychobiological Theory of Personality is the most appropriate theory for this research and is therefore used as the framework for this study. It clearly proposes a relationship between a specific temperament dimension and a specific neurotransmitter (Baeken, Bossuyt, & De Raedt, 2014). This is an essential assumption in this study. It hypothesizes that a single neurotransmitter, serotonin, plays an important role in the proposed association between the HA temperament and migraine. Although it is not as simple as a one-to-one interaction, this assumption is necessary in order to investigate this hypothesis. This theory also provides both biological and psychological perspectives of

personality which mirrors the influences on migraine. Migraine clearly has biological influences, but the cognitions and emotions of the individual also play a role in this disease (Brandes, 2008; de Araújo, Barbosa, Lemos, Domingues, & Teixeira, 2012). Using this theory thus allows for the investigation of a reductionist hypothesis whilst still accepting that there is not a simple aetiology or relationship. Furthermore, there is a need for coherency in the field of personality psychology where the lack of a decided conceptualization and operationalization has made comparison difficult (Corr & Matthews, 2009). Cloninger's theory has been used in similar investigations and therefore should be used in this study as an aim of this research is to add to the literature in this area.

2.4. Temperament and emotion regulation

The circumstances of the human experience inevitably change and to meet the demands of this fluid existence, individuals need to make behavioural adjustments as alterations in circumstances are assessed, consciously or unconsciously, to have either a positive or a negative impact for the individual. This assessment initiates a transient response system, with several components, known as an emotion. These adaptive devices alert human beings to an opportune moment or to signal potential harm (Garland et al., 2010). Dysregulation reduces the functionality of these emotions, yielding instead a source of dysfunction. This inability to control emotions adequately could also become a forerunner for the development of psychopathology (Eisenberg et al., 1996; Fox & Calkins, 2003; Garland et al., 2010).

Regulation of emotion is a skill which develops early in life in order to facilitate healthy social behaviour (Eisenberg, Fabes, Guthrie, & Reiser, 2000; Fox & Calkins, 2003).

Emotional regulation was defined by Eisenberg et al. (2000, p. 137) as “the process of initiating, maintaining, modulating, or changing the occurrence, intensity, or duration of internal feeling states and emotion-related physiological processes, often in the service of accomplishing one's goals”. The development of this skill is shaped by both extrinsic factors and intrinsic factors. The most important of the latter, and the focus of this study, is temperament (Fox & Calkins, 2003; Stadler et al., 2007).

Temperament is defined as the individual's automatic emotional reactions and habits and develops early in life, unaffected by sociocultural learning (Cassimjee & Murphy, 2010; Cloninger et al., 1998, 1993; Ettelt et al., 2008). It is considered to be a stable and heritable element in psychological make-up (Celikel et al., 2009; Cloninger et al., 1998, 1993; Ettelt et al., 2008; Gois, Akiskal, Akiskal, & Figueira, 2012; Määttänen et al., 2011; Merwood, Asherson, & Larsson, 2013) and is frequently associated with the development of psychopathology (De Pauw & Mervielde, 2010; Nigg, 2006).

The four temperament dimensions proposed by Cloninger are involved in the cognitive controlling of emotion and behaviour (Stadler et al., 2007; Verweij et al., 2010). Each temperament dimension is theoretically underpinned by a neurobiological system (Verweij et al., 2010; Zuckerman, 1995). Neurotransmitters regulate communication between neurons of a given neuronal pathway by controlling action potentials. Neurotransmitters are in turn governed by specific enzymes (Zuckerman, 1995). Dysregulation of these neurobiological systems could disrupt temperament, and thus emotional regulation. It has been reported that high scores in the HA trait, as well as low scores in NS, RD, and P, represent individuals who are most at risk with regards to physical and mental health (Wessman et al., 2012). The HA temperament dimension is a focus in this study.

2.5. Harm Avoidance

HA is thought to reflect variation in the BIS of the brain (Cloninger, 1987) and this measure correlates with the BIS referred to in Gray's Reinforcement Sensitivity Theory (Mardaga & Hansenne, 2007). In Cloninger's theory this system includes the septohippocampal system, serotonergic projections from the raphe nuclei in the brain stem, and cholinergic projections to the frontal neocortex from the ventral tegmental area and the basal nucleus of Meynert (Cloninger, 1987).

HA has been particularly associated with migraine (Di Piero et al., 2001; Mongini et al., 2005; Sánchez-Román et al., 2007). Individuals that score higher than average in HA are typically pessimistic, cautious, tense, inhibited, easily tired due to low energy levels, worrying, anxious with a tendency to predict failure rather than success, have an aversion to risk-taking, and exhibit difficulty with unfamiliar situations or changes (Cassimjee & Murphy, 2010; Cloninger, Svrakic, & Przybeck, 2006; Cloninger, 1987; Conrad et al., 2007; Ismael & Baltieri, 2014; Mazza et al., 2009; Vaughn, DeLisi, & Matto, 2014). These individuals are assumed to be particularly attuned to signals of punishment or newness (Farmer & Goldberg, 2008a).

2.6. Harm Avoidance and psychopathology

HA has been associated with both depression and anxiety (Ball, Smolin, & Shekhar, 2002; Engström, Brändström, Sigvardsson, Cloninger, & Nylander, 2004; Knaster, Estlander, Karlsson, Kaprio, & Kalso, 2012; Mochcovitch et al., 2012). This was investigated in the study by Ball et al. (2002), where 120 patients as well as 17 healthy participants completed

the Temperament and Character Inventory, the Beck Anxiety and Beck Depression Inventories, the Anxiety Sensitivity Index (ASI), the Personality Disorders Questionnaire-Revised (PDQ-R), and the Strategic Approach to Coping Scale (SACS). The 120 patients were grouped based on their Axis I diagnosis: Primary panic disorder (37.5%), generalized anxiety disorder (14%), social phobia (11%), obsessive-compulsive disorder (10%), primary depressive disorder (17.5%), and Other Anxiety – primary specific phobia or anxiety phobia not otherwise specified (10%). Since their study is reliant on the accuracy of the diagnoses, a limitation of the study by Ball et al. (2002) is that they did not carry out inter-rater reliability. However, there was interviewer training beforehand and the mean scores of the participants on their self-report questionnaires were comparable to the measurement profiles in other studies for the various diagnoses. Further, the diagnosis category and number thereof were not associated with specific raters. Results of the study by Ball et al. (2002) indicate that except for the Other Anxiety group, all patients showed higher HA scores than the normal controls ($p < .001$). The Other Anxiety group also had significantly lower scores on the HA dimension than both the generalized anxiety disorder and depression groups. There were no other significant differences between the diagnostic groups on the other temperament dimensions. Therefore, their study supported the association between anxiety and depression and the HA dimension as well as the lack of association between these two disorders and the other three temperaments (Ball et al., 2002).

With regards to depression in particular, the HA temperament dimension has been related to a higher risk for developing depression, the severity of depressive symptoms with which a patient presents, and to treatment response (de Melo Santos et al., 2011; Farmer & Seeley, 2009; Kampman & Poutanen, 2011). The influence of depression on HA was also investigated in the study by Ball et al. (2002). When comparing the HA scores of the control

group ($n = 17$) with the depression group ($n = 21$) there was a significant difference between the former ($M = 0.29$, $SD = 0.13$) and the latter ($M = 0.68$, $SD = 0.22$). Engström et al. (2004) investigated personality using the TCI in 100 bipolar euthymic patients (male = 60, female = 40, $M_{age} = 55.8$, $SD = 14.3$) and 100 controls ($M_{age} = 54.8$, $SD = 14.7$) matched for age and gender. The total bipolar group, even when clinically euthymic, showed higher HA scores than the control group with a moderate effect size ($d/s = 0.34$, $p = .020$) (Engström et al., 2004).

In addition, the 120 patients in the study by Ball et al. (2002) were grouped based on comorbidity: No other comorbid psychiatric conditions (41%), comorbid anxiety diagnosis (26%), and comorbid anxiety and depressive disorders (33%). A significant effect for only the HA dimension was found for comorbidity ($F(2, 117) = 13.91$, $p < .001$). Tukey post-hoc tests indicated that patients with depression had significantly higher HA scores and significantly lower SD scores than either the no comorbid or comorbid anxiety groups ($p < .001$). In order to ascertain the separate effects of severity and depression, a stepwise multiple regression analysis was performed on the HA scores: First severity index and then comorbidity type. Severity ($t = 3.79$, $p < .001$) and comorbid depression ($t = 3.4$, $p < .001$) both contributed independently to predicting HA scores ($R = 0.53$, $p < .001$). This indicates that comorbid depression, and not comorbidity of a second anxiety disorder, relates to increased HA scores independent of illness severity (Ball et al., 2002).

The relationship between HA and depression has also been indicated in a South African sample. Peirson and Heuchert (2001) investigated the relationship between personality and mood, assessed using the TCI and Beck Depression Inventory (BDI) respectively, in 471 undergraduate psychology students ($M = 111$, $F = 360$, $M_{age} = 20.32$,

$M_{age} F = 19.19$) from the University of the Witwatersrand, Johannesburg. A moderate significant correlation was indicated between BDI score and HA score ($r = .44, P < .001$) which suggests that HA is related to a depressed mood state. This study also showed a strong significant inverse relationship between BDI score and S ($r = -.54, P < .001$), as well as low but significant relationships between BDI score and RD ($r = -.14, P = .002$), P ($r = -.11, P = .023$), and C ($r = -.26, P < .001$) (Peirson & Heuchert, 2001). An exclusion criterion of a psychiatric diagnosis was not reported, but the results of this study support a relationship between HA and a lowered mood state.

Four possible relationships between HA and depression have been identified. Firstly, depression as a state impacts a trait measure (HA) (Hansenne & Bianchi, 2009; Margetić & Jakovljević, 2013). It has been shown that the HA trait is influenced by the mood or anxiety state of the individual. For example, Chien and Dunner (1996) assessed the stability of TPQ scores in clinically depressed outpatients taking part in pharmaceutical trials. Patients completed both the TPQ and 17-item Hamilton Depression Rating Scale (Ham-D₁₇) before and after the 12-week treatment trial. Out of 63 patients ($M = 30, F = 33, M_{age} = 42.3 \pm 11.8$), 35 (55.6%) responded to treatment as indicated by an improvement on the Ham-D₁₇ score to 10 or a 50% decrease in their baseline score. Twenty-eight (45.4%) did not respond to treatment. Eight patients were given placebos throughout the trial, 6 in the non-responder group and 2 in the responder group. In the responder group, the global and subdimension HA scores were significantly lower at the end of the 12-week trial. Non-responders showed no significant differences in NS, HA, and RD scores. The authors concluded that the HA personality trait reflects changes in affective state (Chien & Dunner, 1996). It has also been indicated that depression expression is influenced by HA (Hansenne & Bianchi, 2009; Margetić & Jakovljević, 2013; Peirson & Heuchert, 2001). Thirdly, the vulnerability model

states that an individual with a structural vulnerability is more likely to be impacted in a negative manner by a stressor. This vulnerability may be temperamental, physiological, endophenotypic, or genetic (Belsky & Pluess, 2009; Bunce & Coccaro, 1999). In this case, HA acts as a risk factor for depression (Farmer & Seeley, 2009; Hansenne & Bianchi, 2009; Margetić & Jakovljević, 2013; Rodríguez-Cano et al., 2014). And lastly, a scar model whereby HA scores would be high even after the individual has entered remission of acute depressive symptoms (Farmer & Seeley, 2009; Margetić & Jakovljević, 2013). Although depression is not directly assessed in this study, it is important to note that HA interacts with the mood state of the individual.

A high score on the HA dimension has also been linked to anxiety disorders (de Melo Santos et al., 2011; Ettelt et al., 2008; Kampman, Viikki, Järventausta, & Leinonen, 2014; Miettunen, Veijola, Lauronen, Kantoj, & Joukamaa, 2007; Wachleski et al., 2008). This could be a result of predisposition caused by an excess of the pessimism and worry associated with HA (Tuominen et al., 2013). Again, it is important to note the interaction between HA and the individual's emotional state.

HA, as well as other temperament and character dimensions in Cloninger's theory have been suggested as vulnerabilities for the development of emotional disorders (Gawęda & Kokoszka, 2014). Extending this argument, due to common genetic influences in anxiety and depression, Ball et al. (2002) postulated that the HA temperament may be the "shared genetic expression of this genetic vulnerability for 'internalizing' disorders" (Ball et al., 2002, p. 102). However, this is beyond the scope of the current study and instead we focus on the impact the associations between HA, depression, and anxiety have for those suffering from chronic pain.

2.7. Harm Avoidance, psychopathology, and pain

The correlation between HA and affective and anxiety disorders has implications for individuals who suffer from a chronic pain disorder such as migraine. Depression, anxiety, and HA have all been purported as important factors in how an individual perceives pain (de Melo Santos et al., 2011; Kim et al., 2004; Villani et al., 2010). Bussone and Grazzi (2013) have proposed an intriguing hypothesis regarding the relationship between emotion and pain perception. They first noted the overlap between brain structures and systems related to emotion and to pain. They proposed that chronic pain is the sign of an imbalance in the homeostasis of the interoceptive system. This system integrates nociceptive (pain) information with emotional consciousness. This could also lead to adaptive behavioural responses. The authors also noted that this hypothetical relationship between emotion and pain means that personality traits should be taken into account when predicting chronic pain (Bussone, Grazzi, & Panerai, 2012; Bussone & Grazzi, 2013). Therefore, the HA temperament is not only related to the mood and emotional state of the individual, but to their experience of physical pain as well.

Gerra et al. (2000) suggested that the relationship between HA and the development of affective disorders could be based on serotonergic dysfunction. A similar proposal was made by Boz, Gazioglu, Altunayoglu, and Hocaoglu (2007) when the results of their study indicated correlations between BDI scores and HA scores ($r = 0.479$, $p < .001$) as well as with SD scores ($r = -0.370$, $p < .001$) in patients with chronic tension-type headache ($N = 50$). Further, it has been reported that certain selective serotonin reuptake inhibitors (SSRIs), a treatment option used for depression, decreased HA scores (Melke et al., 2003). It could be speculated that the treatment of depression could reduce HA and thereby adjust pain

perceptions in patients with chronic pain, thus helping to attain pain control (Pud et al., 2006, as cited in de Melo Santos et al., 2011). It has been noted that anxiety has been related to low levels of serotonin (Corr & Matthews, 2009), as has depression (Elliott, Zahn, Deakin, & Anderson, 2011). As the serotonin neurotransmitter is also theoretically related to HA, it is plausible that it is involved in the associations between anxiety, depression, and HA.

Reducing HA through treatment may seem contradictory to the assumption that temperament traits are relatively stable and heritable. However, consider the following with regards to pain: According to Cloninger's theory, genetic variation of the temperaments follows a normal distribution with the majority of individuals falling within the average range (Cloninger, 1987). The HA dimension serves as a modulator of both NS and RD. This leads to active inhibition of exploratory behaviour towards novel or uncertain situations (NS) as well as passive avoidance of stimuli associated with punishment or non-reward (RD). This modulatory attribute allows the environmental influence on HA to have an effect on all three temperaments. For example, when confronted with a novel stimulus, HA tends towards inhibition of seeking behaviour or passive avoidance behaviour whereas NS leads towards active approach behaviour. It is the influence of the environment which determines the balance between the temperaments and therefore the behaviour (Cloninger, 1987). Therefore, although the genetic formation of the temperament traits is independent, the environment can have an influence (Cloninger, 1987) and experience influences an individual's adaptive tendencies (Cloninger, Przybeck, & Svrakic, 1991). The pain experienced during a migraine attack, as well as the accompanying thoughts and behaviour regarding this pain in between attacks and depression and anxiety, could be a circumstance in which the balance is tipped towards the HA temperament which results in a greater influence of this dimension.

Therefore, an individual who scores high in the HA dimension may show even higher scores when coping with this circumstance.

These possible interactions between HA, affective and anxiety disorders, the serotonin neurotransmitter, and perception of pain are herewith discussed, and are also depicted in Figure 2.5.

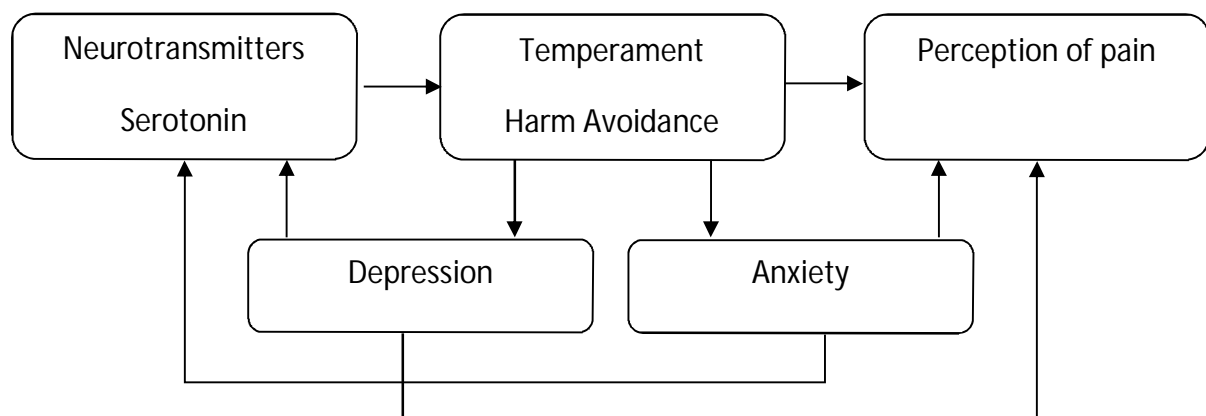


Figure 2.5. Proposed interactions between HA, depression, anxiety, the serotonin neurotransmitter, and perception of pain.

Gustin, Burke, Peck, Murray, and Henderson's (2016) study is the first to compare personality characteristics between patients in the two main categories of chronic pain. Their study compared patients suffering neuropathic and nociceptive chronic pain in the same body region, avoiding the influence of body region on psychological and behavioural responses to chronic pain, in order to support the existence of a mutual pain personality. Thirty-seven healthy female controls ($M_{age} = 51.8 \pm 2.0$) were compared to 32 female patients with chronic orofacial pain ($M_{age} = 53.8 \pm 1.8$) diagnosed with either painful trigeminal neuropathy (PTN) ($n = 17$, $M_{age} = 55.0 \pm 2.2$) or painful temporomandibular disorder (TMD) ($n = 15$, $M_{age} = 52.5 \pm 3.1$). The authors excluded patients taking serotonergic antidepressants so as to avoid

extraneous influences on HA and SD scores. In comparison to the control group, both pain groups had significantly higher scores in the global HA scale (TMD vs CON: $P = .000$, PTN vs CON: $P = .000$) as well as in the two subdimensions HA1 (TMD vs CON: $P = .001$, PTN vs CON: $P = .000$) and HA4 (TMD vs CON: $P = .003$, PTN vs CON: $P = .005$). Between the two pain groups, there were no significant differences in the HA scale nor in any of the HA subdimensions. Furthermore, both pain groups and the control group were compared to normative values from a standard community sample of 300 normal adult individuals. Only the pain groups had higher values in HA, HA1, HA3, and HA4. Their study also indicated that both pain groups had significantly lower scores in the SD1 subdimension (TMD vs CON: $P = .000$, PTN vs CON: $P = .000$) with TMD patients also showing lower scores in the SD2 subdimension ($P = .002$). A pain personality typified by high HA and low SD was therefore indicated by this study (Gustin et al., 2016). A personality profile including high HA may have implications for how the individual copes with stress. In this case, pain as a stressor.

The suggestion has been made that an individual's coping style is born from the interaction between their temperament and their experience (Ravaja, Keltikangas-Järvinen, & Kettunen, 2006). This indicates that temperament and the experience of pain could dynamically interact (Ravaja et al., 2006). Gustin et al. (2016) propose that individuals high in HA could pessimistically, negatively, and fearfully anticipate pain leading to ruminating thoughts and an eventual cycle of chronic disability and suffering which worsens the pain. Furthermore, this process could lead to a lowered mood as well as anxiety which are associated with an increase in HA and a decrease in serotonin. Therefore, it is plausible that temperament, pain, affective and anxiety state, and serotonin are interacting factors.

With regards to serotonin, it has been proposed that projections of the serotonergic system may mediate coping responses to aversive events, acute (proximal or distal) or chronic. An acute proximal aversive event is unconditioned and results in a fight-flight response. Pain is included within this category. Conversely, acute distal aversive events are conditioned and are warnings of pain. These warnings are detected in the form of visual, auditory, and olfactory senses and can lead to anticipatory anxiety. If the aversive event cannot be staved off or eliminated using defence mechanisms then the event is categorized as chronic (Deakin, 1998).

Furthermore, Strelau (2001) noted that the neurobiochemical mechanisms resultant in temperament is subject to slow change. This change is as a result of maturation as well as the genotype-environment interaction specific to the individual (Strelau, 2001). A genetic predisposition to a temperament with a negative perception of punishment, for example pain, could then interact with negative stimuli from the environment. Although this is a task for future studies, there is the potential for a model incorporating temperament, genotype, pain, depression, anxiety, and serotonin.

2.8. Summary of chapter

Personality research has a long history and common terms frequently used within it were developed over several decades. In particular, trait and temperament are two constructs which are currently used somewhat interchangeably but whose development was fundamentally different. In this dissertation, both temperament and trait are used to refer to the biological and innate tendency to react in a certain way to various stimuli. This chapter also discussed a number of theories of personality which, despite their differences, have

several commonalities. However, Cloninger's Psychobiological Theory of Personality is uniquely suited for this study as it incorporates both biological and psychological dimensions which are differentiated by the learning process of each. The effect of learning further allows for an iterative process whereby the temperament dimension profile of the individual can differ as a result of their circumstances. One such circumstance is chronic pain where HA could be elevated due to an increased desire to avoid harm. It is proposed that HA, and its corresponding neurotransmitter serotonin, is influential in how an individual responds to pain and their learnt behaviour or coping. The possible interactions between these factors are further elaborated in the next chapter with regards to migraine.

CHAPTER 3: MIGRAINE AND TEMPERAMENT

In this chapter, the roots of the “migraine personality” are first discussed as well as the psychological implications this could have for the individual. In order to link to the argument in the previous chapter, the literature regarding relationships between HA, migraine, and the serotonin neurotransmitter is discussed. Currently, there are few decisive conclusions in this area. Therefore, an attempt is made to cover literature on both sides of each argument before making a final inference. Lastly, a migraine model is proposed.

3.1. Migraine personality

The migraine headache disorder was ranked as the 3rd most prevalent disorder and the 7th most debilitating disorder internationally by the Global Burden of Disease Survey 2010 (Headache Classification Committee of the International Headache Society (IHS), 2013). In South Africa, nine million individuals suffer from headaches and migraines regularly. It is more prevalent in females, 18% of South African women, compared to males, 6% of South African men (Leaders in Wellness: The Business of Health, 2014).

Most migraine definitions have included core features: A recurrent, one-sided, throbbing headache lasting 4-72 hours, worsened by physical activity and associated with gastrointestinal symptoms and photophobia and/or phonophobia (Headache Classification Committee of the International Headache Society (IHS), 2013; Low, Merikangas, & Merikangas, 2004; Schürks, Buring, & Kurth, 2010). According to the International Headache Society (IHS) there are two main subtypes of migraine: Migraine without aura (MO) and migraine with aura (MA) (Headache Classification Committee of the International Headache Society (IHS), 2013; Olesen, 2004). This dissertation focuses on MO, the most

common form of migraine (Ozge et al., 2015), for which the diagnostic criteria are listed in Table 3.1 (Headache Classification Committee of the International Headache Society (IHS), 2013).

Table 3.1.

International Headache Society diagnostic criteria for migraine without aura

- A. At least 5 attacks fulfilling criteria B–D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
 1. Unilateral location
 2. Pulsating quality
 3. Moderate or severe pain intensity
 4. Aggravation by or causing avoidance of routine physical activity
- D. During headache at least one of the following:
 1. Nausea and/or vomiting
 2. Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society (IHS) (2013)

An association between headaches and psychiatric disorders has also been documented for centuries (Antonaci et al., 2011; Gentili et al., 2005; Pompili et al., 2010). In 1895, Living noted both mood and cognitive symptoms in patients with migraine (Gentili et al., 2005). The former included depressed mood and irritability whilst the latter encompassed memory and attention deficits. Following this, in 1937, Wolf (as cited in Merikangas, Merikangas, & Angst, 1993) documented the ‘migraine personality’. This incorporated the dominant personality traits and reactions observed in migraine patients and was trademarked by anxious and depressive traits (Gentili et al., 2005; Merikangas, Merikangas, et al., 1993; Merikangas, Stevens, et al., 1993; Pompili et al., 2010). It was believed that these traits result in negative emotional reactions which trigger migraine manifestation. Therefore, these personality traits were hypothesized to increase vulnerability to migraine (Merikangas, Stevens, et al., 1993).

In Cloninger's theory, individuals who score high on the HA dimension are typically pessimistic, cautious, careful, fearful, tense, apprehensive, inhibited, easily tired due to low energy levels, worrying, anxious with a tendency to predict failure rather than success, have an aversion to risk-taking, and exhibit difficulty with unfamiliar situations or changes (Cassimjee & Murphy, 2010; Cloninger et al., 2006; Cloninger, 1987; Conrad et al., 2007; Ismael & Baltieri, 2014; Kose, 2003; Mazza et al., 2009; Vaughn et al., 2014). Given the parallels between personality characteristics typical of HA and of migraine, it is considered likely that migraineurs would demonstrate higher HA scores. In addition, anxiety and affective disorders have been related to both migraine (Abbate-Daga et al., 2007; Erten, Yenilmez, Fistikci, & Saatcioglu, 2013; Just et al., 2003; Kristensen, Mortensen, & Mors, 2009; Miettunen et al., 2007; Oedegaard et al., 2006; Paavonen et al., 2014) and HA (Storage et al., 2013). However, investigations into a connection between the temperament dimensions and migraine have been conflicted where HA, and other dimensions, has been inconsistently found to be associated with migraine (Abbate-Daga et al., 2007). This is discussed now.

3.2. Migraine and Harm Avoidance

HA scores are reportedly higher in migraine patients when compared to healthy controls. Di Piero et al. (2001) compared the temperament scores of patients with migraine ($n = 121$) or with tension-type headache ($n = 42$) with the normative data collected for each temperament dimension. The results indicated that the HA score for each group was higher than the reference values ($p < .001$). In addition, migraineurs showed a significantly lower score on the NS temperament scale ($p < .001$) (Di Piero et al., 2001). When Mongini et al., (2005) compared 49 women with migraine and 49 controls, the migraine group scored significantly higher than the controls in HA ($p < .001$) and P ($p < .05$). Park, Han, Yang, Kim,

and Lee (2006) compared MO patients ($n = 97$, $M_{age} = 45.8$, $SD = 9.5$) and controls ($n = 100$, $M_{age} = 48.3$, $SD = 9.0$) and also noted significantly higher HA scores in the former group ($p < .001$). Sánchez-Román et al. (2007) further corroborated with these three studies and reported an increased HA score in migraine patients compared to two different types of healthy controls ($p < .05$). Taking these studies into consideration there does appear to be a temperament component in migraine, including an increased HA score.

Furthermore, in their investigation of the “repeater phenomenon”, referring to patients who visited the emergency department at least three times at least a week apart within a six-month period, Villani et al. (2010) claimed that their investigation provided evidence of such an association. Of the 465 migraine patients included in their study, 70 (15%) (male = 13, female = 57, $M_{age} = 36.4$, $SD = 10.0$) met the repeater criteria. The assessment battery included the TPQ. On this measure, repeater migraineurs scored higher on the HA temperament scale and subdimensions than the non-repeater patients ($p < .001$). There were no significant differences observed between the two groups for the other scales of the TPQ (Villani et al., 2010).

However, results negating a relationship between HA and migraine have also been reported. The study performed by Nylander et al. (1996) used a Swedish family with members suffering from migraine as the sole population from which the sample was taken. Of the 103 family members assessed, excluding migraineurs who had married into the family and their children in an attempt to control for genetic heterogeneity, there were 29 migraine participants. Three of the latter did not complete the personality questionnaire. The authors failed to find a difference in any of the four main temperament scores between migraine ($n = 26$, male = 11, female = 15, age range = 20-78) and the age- and sex-matched control group

($n = 87$), finding instead a difference in two NS subdimension scores. The NS1 subdimension (exploratory excitability) score was slightly higher than the control group score whilst the NS2 subdimension (impulsivity) score was significantly higher in the migraine group ($p = .0448$) (Nylander et al., 1996). Although Nylander et al. (1996) claim that the use of a single family with an autosomal dominant inheritance pattern of migraine would highlight an association between certain personality traits and migraine, it limits generalizability and comparison of their findings. Furthermore, the control group was shown to be representative of the general population but were recruited from the same northern Sweden area as the migraine participants. This suggests that environment could have influenced the results.

Boz et al. (2004) also failed to demonstrate a link between migraine and HA when comparing migraine patients ($n = 51$, 46 MO, 5 MA) and controls ($n = 82$). The authors put forward that this could be explained by the high prevalence of migraine and tension-type headache (TTH) coexistence. Individuals with both disorders have displayed higher neuroticism scores whereas those with a diagnosis of only migraine have not. Hence, the existence of a connection between migraine and personality could be due to the comorbidity of TTH (Boz et al., 2004).

In conclusion, there has not yet been an unequivocal conclusion drawn regarding this possible association as the available results, only a few discussed here, conflict. However, the association between migraine and HA remains reasonable and Cloninger's theory is able to connect each temperament trait with a biological foundation and thereby allows for a mechanism by which a psychological experience can manifest as a physiological response, and *vice-versa* (Määttä et al., 2011). This refers to the neurobiological systems which are discussed.

3.3. Harm Avoidance and the serotonin neurotransmitter system

According to Cloninger's theory, the described temperament traits are underpinned by different neurobiological systems, with HA associated with serotonergic activity (Conrad et al., 2007; Di Piero et al., 2001; Hennig, Toll, Schonlau, Rohrmann, & Netter, 2000; Paavonen et al., 2014). Serotonin, or 5-hydroxytryptamine (5-HT), is an inhibitory neurotransmitter (Schwedt, 2007; Tuominen et al., 2013) and serotonergic neurons innervate several cortical structures. Of these structures, the area most populated with serotonin neuron terminals and 5-HT receptors is the frontal lobe. This high density indicates that 5-HT plays a role in the functions of the pre-frontal cortex, such as cognition and emotional control (Baeken et al., 2014; Celada, Puig, & Artigas, 2013). As temperament is involved in emotional control, this supports a possible relationship between HA and temperament. The association between HA and the serotonin neurotransmitter is also in keeping with the hypothesis put forth by Deakin (1998) and later Tops, Russo, Boksem, and Tucker (2009) which stated that the serotonergic system mediates a drive to withdraw from situations which are considered harmful, unpleasant, or overly stimulating.

A South African study further found that patients suffering social anxiety disorder (SAD) ($n = 63$, male = 35, female = 28) had higher HA scores when compared to controls ($p < .001$) (Lochner et al., 2007). This indicates that HA and aspects of anxiety symptoms may be underpinned by a common neurotransmitter system (Cassimjee & Murphy, 2010). Given the associations between serotonin and affective and anxiety disorders, and between serotonin and HA, it is hence postulated that this system would play an integral role in a model of these variables and their relationships.

However, the hypothesis of one neurotransmitter underlying one temperament has been a source of disagreement in the literature for several years and union has still not occurred. Several of these studies are discussed herein, indicating both opposition and support for a genetic basis of personality. HA and its corresponding serotonin are the main focus as this temperament dimension has often been implicated in migraine. Zuckerman (1995) agreed with the assumption that behavioural inhibition is associated with the neurotransmitter serotonin, but maintained that it was too simplistic to assume that a temperament dimension is solely associated with a single neurotransmitter. He suggested an alternative explanation where, rather than relying on a single neurotransmitter concentration, there could be interactions between neurotransmitter systems, and moreover the hormones and enzymes regulating these systems, resulting in the observed temperament trait. Therefore, it was acknowledged that there was support for a biochemical basis for an individual's personality, but it was more complex than previously proposed (Zuckerman, 1995).

Interactions were also suggested by Cloninger (1987), but a key difference is the level at which these proposed interactions occur. Zuckerman (1995) maintained that interactions occur at the level of the neurotransmitter systems to influence one temperament trait. However, as noted by Stallings et al. (1996), Cloninger (1987) suggested that the temperament traits themselves interact to form the differing behaviour resultant from personality variation. In this train of thought, the temperament dimensions are biogenetically predisposed independently but are able to influence each other through their interactions to determine behavioural responses to punishing, rewarding, and novel stimuli (Cloninger, 1987; Stallings et al., 1996). For example, HA is a moderating influence on both NS and RD: Inhibition of exploration of new situations and passive avoidance of punishment and non-reward. Therefore, two individuals may have the same response level for a certain

temperament dimension, e.g. NS, but can be differently expressed by each as the response levels of the other dimensions, e.g. HA, have an impact (Stallings et al., 1996). This does not preclude interaction at the level of the neurotransmitter systems, but places an emphasis on interaction between the temperament dimensions as determinants of personality variation. Neurotransmitter interaction was, however, supported in the study by Ruegg et al. (1997).

Ruegg et al. (1997) examined the relationship between temperament dimensions and the prolactin and cortisol responses to administration of intravenous clomipramine in 32 healthy participants. Clomipramine is a SSRI and would therefore cause a functional response from the serotonergic system. This would be reflected in the responses of prolactin and cortisol. As expected, the cortisol response correlated only with HA, the temperament dimension supposedly underpinned by the serotonergic system. However, prolactin was negatively correlated with NS and only positively related to HA in a *post hoc* analysis. The authors postulated that the prolactin response was influenced by the dopaminergic system (Ruegg et al., 1997). This supports the possible interaction between the neurotransmitter systems.

This line of thought was followed by Widiger et al. (2006) who commented that there are several obstacles which limit the likelihood of identifying a simple one-to-one relationship between a neurotransmitter system and a temperament dimension. Firstly, the complexity of the neurotransmitter systems should be taken into account as well as the need for further research within neurochemistry. Both these factors make finding this relationship improbable. Secondly, it was noted that due to this complexity it is more likely that a specific neurotransmitter system would be related to a narrower concept than to a single, broad temperament dimension. Therefore, although it may be an ideal to identify traits

corresponding with a genetic structure it was deemed as unlikely that correlates would be found given the intricacy of brain systems (Widiger et al., 2006).

There have also been inconsistencies in reports where studies have investigated the genetic basis of personality and the neurotransmitters proposed to be involved (Nyman et al., 2009). In their study, Herbst, Zonderman, McCrae, and Costa Jr (2000) assessed whether NS and HA as measured by the TCI were related to functional polymorphisms of the D4 dopamine receptor gene and the serotonin-transporter-linked promoter region, respectively. Their study found no support for the model in line with other research (Ham et al., 2004; Kusumi et al., 2002; Munafò et al., 2009; Samochowiec et al., 2001; Tuominen et al., 2013), and in contradiction of other studies which have indicated a relationship between genetic structure and temperament dimensions (Blaya et al., 2009; Melke et al., 2003; Na et al., 2011).

As an example of the latter, Nyman et al., (2009) investigated temperament dimensions and all known dopamine receptor genes, DRD1-DRD5, in a Finnish sample ($N = 1434$). This provided a comprehensive view of the dopamine receptor gene family. NS and HA (in women) were associated with two single nucleotide polymorphisms (SNPs) of the DRD2 receptor gene. These variations had putatively opposite effects on NS and HA: The variants associated with low NS were also associated with high HA. Also on the DRD2 receptor gene, four SNPs were found to be associated with P in women. Although this supports a genetic basis for three temperament traits, it is not entirely consistent with Cloninger's model where only NS is associated with the dopamine neurotransmitter. However, this study used uncorrected values as the results were insignificant when using

corrected values. This indicated that further research is required as to why dopamine would be related to all three temperaments rather than NS alone (Nyman et al., 2009).

Furthermore, in a study using a clinical sample ($N = 164$), Lin et al., (2010) investigated genotype and temperament in bipolar I (BP-I) ($n = 47$) and II (BP-II) ($n = 61$) patients and controls ($n = 56$) as both genetic and personality influences in susceptibility to these disorders are reported. For both BP-I and BP-II groups, the NS and HA scores were significantly increased compared to the control group. Furthermore, an interaction between NS and a polymorphism of the dopamine D3 receptor gene was exhibited in BP-I patients only. This indicated that there is a genetic component in moderating the relationship between NS and the bipolar disorders (Lin et al., 2010).

There have even been contradictions about the genetic basis for temperament within the same study. Another objective of the study by Herbst et al. (2000) was to assess the Temperament and Character Inventory. In this questionnaire each temperament dimension is measured with several subdimensions and it was proposed that a genetic basis for the temperament dimension would be indicated if the subdimensions covaried. Following this analysis, it was suggested as unlikely that the subdimensions of NS and RD had a common genetic basis as they did not each describe a common factor. HA subdimensions did however covary which would indicate a genetic underpinning (Herbst et al., 2000). This would seem to suggest that while their study did not find a relationship between HA and the serotonin-transporter-linked promoter region there is still support for a genetic basis of HA.

Receptor studies have been performed to assess for an association between serotonin and HA. In the study by Gerra et al. (2000), HA was significantly correlated with

serotonergic function. This correlation was indicated when measuring the effect of D-fenfluramine, a serotonin releaser and agonist, on hormonal release from the hypothalamus-pituitary-adrenal axis (HPA). Increases in both the prolactin (PRL) and cortisol (CORT) hormones indicate involvement of the serotonergic system. HA scores showed significant correlations with PRL ($r = .424, p < .05$) and CORT ($r = .595, p < .005$) Areas Under the Curves (AUCs) (Gerra et al., 2000). AUCs are used when conducting endocrinological or neuroscientific studies in order to obtain information from repeated measurements taken over time (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). However, stimulation of the serotonin receptors and the resultant hormonal response by the HPA axis can only give an indication of the neurotransmitter role in this axis and not the brain as a whole. It can also not distinguish between pre- and post-synaptic action and thus does not provide further information about serotonin concentration. A synapse is depicted in Figure 3.1 below (National Institute on Aging, 2008). Nevertheless, the authors stated that this correlation may provide additional support for the facet of behavioural inhibition in Cloninger's theory (Gerra et al., 2000).

Baeken et al. (2014) explored the relationship between 5-HT_{2A} receptors and HA, specifically targeting the prefrontal cortices, in 26 healthy participants (male:female = 13:13, age range = 18-65). These regions were focused on as they are involved in cognitive processes relating to affective disorders. Their results did not provide any evidence for an association between HA scores and serotonin receptor binding indices (BI) in the anterior cingulate cortex (ACC). However, their results did indicate that HA scores were positively related to the BI of the serotonin receptors in the dorsal prefrontal cortex (DPPFC) (Baeken et al., 2014). This study, therefore, supported the association between the HA temperament and the serotonergic system.

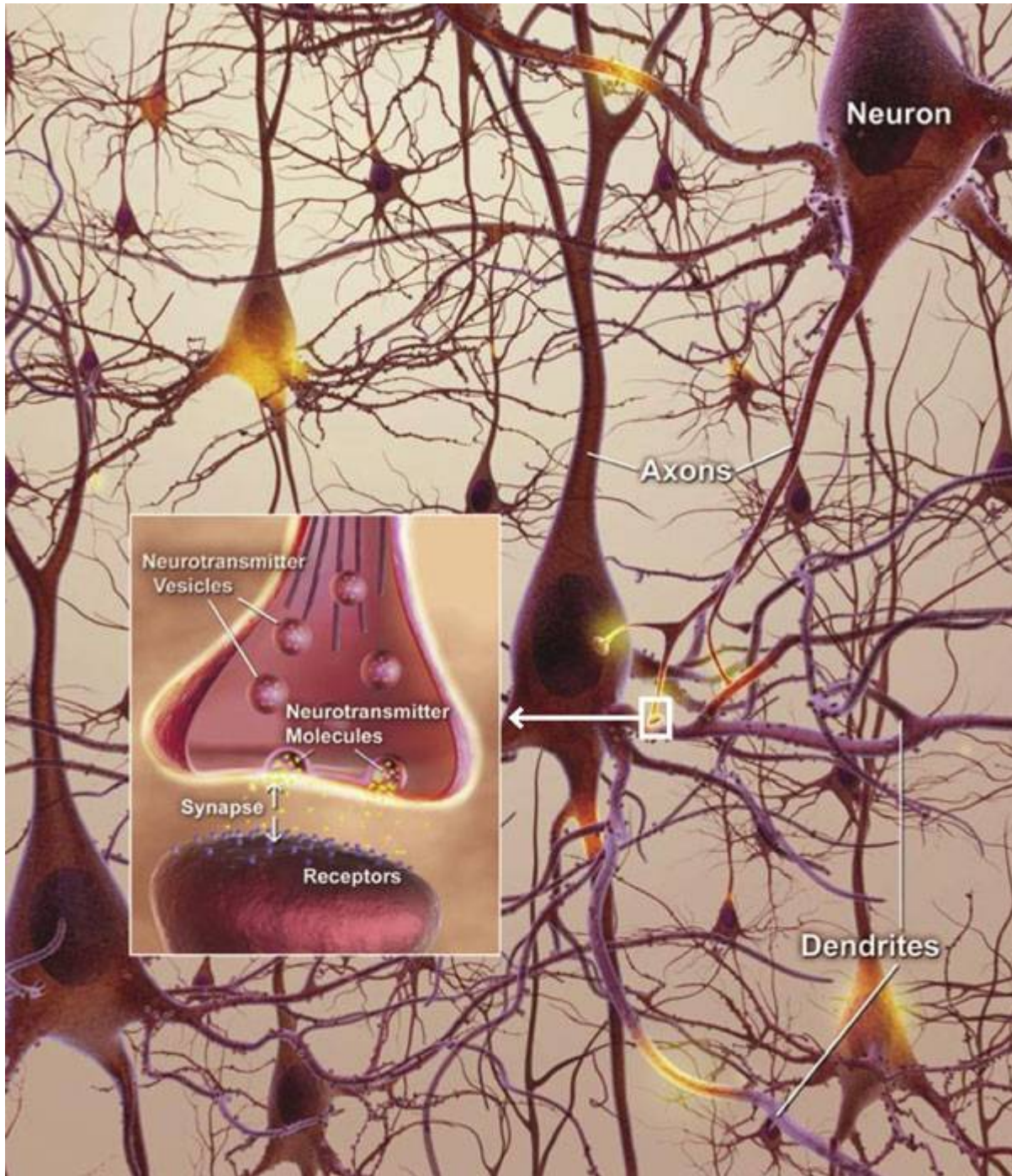


Figure 3.1. Neurons in the brain. Reproduced from *Alzheimer's Disease: Unravelling the Mystery*, by the National Institute on Aging, 2008. Reproduced with permission.

Furthermore, the positive association between HA scores and serotonin receptor BI in the DPFC was reported by Baeken et al. (2014) as consistent with previous studies indicating that serotonin receptors can be upregulated, i.e. the number of postsynaptic receptors

increased, during periods of chronic stress. This increase in receptors may be in response to a low extracellular serotonin concentration. As the functionality of the DPFC area is particularly impacted during dysregulated affective states, the authors suggested that this reflects a potential vulnerability to fear and stress (Baeken et al., 2014). As stated in the previous chapter, HA overlaps with Neuroticism and it is therefore interesting to note that Frokjaer et al. (2008) also hypothesized an association between the personality trait Neuroticism, included in the Five-Factor Theory of Personality, and postsynaptic serotonin receptor binding in the frontolimbic area. As Frokjaer et al. (2008) expected, there was a significant positive correlation [$r(79) = .24, p = .028$], which was strongest for the vulnerability component ($r = .35, p = .009$, Bonferroni corrected). Neuroticism and its vulnerability component are highly correlated ($r = .75-.79$) and therefore the authors assumed that a high vulnerability score, an assessment of stress-coping strategies, is also associated with a higher risk for depression. Frokjaer et al. (2008) proposed that the strong correlation between serotonin receptor binding and vulnerability is an expression of the association between stress and risk of depression (Frokjaer et al., 2008). Therefore, these two studies indicate that personality and serotonin receptors could be involved in an individual's response to stress, such as headaches.

However, in the study by Baeken et al. (2014) the participants were healthy with no history of affective, psychiatric, or neurological disorders. Although depression is associated with a low concentration of serotonin (Hamel, 2007; Robinson, Cools, Crockett, & Sahakian, 2010), studies reducing the concentration of serotonin precursors, and thereby reducing serotonin, indicate that a low concentration of this neurotransmitter is insufficient to result in a depressed mood state (Robinson et al., 2010). It could therefore be hypothesized that a low serotonin concentration could be associated with the temperament HA and yet not lead to

depression until other requirements are met. One of these factors could be stress. Firk & Markus (2007) stated that, despite the possible genetic vulnerability to depression resultant from genetic variation influencing the serotonergic system, it is not the only factor and stress could play a role.

Serotonin is released in response to a stressful stimulus. Serotonin, amongst other neurotransmitters, has been shown to be released in the prefrontal cortex (PFC) following exposure to a stressor (Arnsten, 2009; Mora, Segovia, del Arco, de Blas, & Garrido, 2012). Increased release of serotonin from the amygdala and hippocampus as well as in the nucleus accumbens was also noted by Mora et al. (2012) during stressful conditions. As discussed later in this chapter, it has been indicated that serotonin is released during a migraine attack. This would be in line with the above studies as migraine is considered a stressor (Lake III, 2009). An event is considered a stressor when it compromises homeostasis of the endocrine, physiological, and psychological systems (Andrews, Ali, & Pruessner, 2013).

As is clear from the literature there is still a large amount of disagreement with regards to whether the temperaments are associated with a single neurotransmitter, if a genetic basis for this can be established unequivocally, and the impact of stress. Gillespie et al. (2003) performed a twin study which indicated that additive genetic effects accounted for between 30 and 41% of the total variance in the temperament dimensions. This signifies that additive genes best explain familial aggregation, i.e. the clustering of a certain trait within a family, for each temperament trait. The dissimilar findings reported above and the possibility of additive genes have implications for the differing results obtained regarding HA and if it associated with either a low or high serotonin concentration. This is discussed in further detail below.

3.4. Harm Avoidance and serotonin neurotransmitter concentration

Carver and Miller (2006) noted in their review that several studies investigating serotonin activity and HA in normal participants found a positive association between HA and serotonin concentration. HA was also reportedly associated with high serotonin in the review by Montag (2014). Carver and Miller (2006) however, stated that there have been conflicting results with some studies indicating that HA was related to greater receptor sensitivity. Greater receptor sensitivity implies lower serotonin levels (Carver & Miller, 2006). Similarly, Gardini et al. (2009) as well as Rodríguez-Cano et al. (2014) also note that HA is associated with decreased serotonergic function. Although HA has been noted to be associated with both a low and a high serotonin concentration, it is argued here that a low concentration would be more likely.

HA has been associated with both depression and anxiety. Serotonergic system dysfunction resulting in a low concentration of serotonin has been implicated in depression (Hamel, 2007; Nakamura & Wong-Lin, 2014). Most of the currently available antidepressant treatments block the 5-HT transporter and increase the synaptic 5-HT concentration. In so doing, serotonin levels, both inside and outside the cell, are increased (Celada et al., 2013; Schwedt, 2007). Due to the common element of altered serotonergic system activity in both HA and depression, one would expect a lower serotonin concentration to be associated with HA. Furthermore, some of the anxiolytic drugs used to treat anxiety are 5-HT_{1A} receptor agonists (Celada et al., 2013). This would indicate that anxiety is also related, and therefore perhaps HA, to a low concentration of the serotonin neurotransmitter. Thus a low concentration of serotonin associated with HA would be probable.

3.5. Migraine and the serotonin neurotransmitter

Serotonin has previously been a focus point in studies investigating the neurobiological systems involved in personality as it is known to be involved in several heritable psychopathologies (Harro et al., 2009). Serotonin has also been implicated in the pathophysiology of migraine (Abbate-Daga et al., 2007; Boz et al., 2004; Panconesi, 2008; Park et al., 2006; Sánchez-Román et al., 2007; Schürks et al., 2011). Suggestions regarding how serotonin exerts an influence on this process include migraine as a disease linked to dysfunction of serotonergic innervation of vessels in the brain (Boz et al., 2004; Hamel, 2007), and migraine as a thrombocyte disease where the storage and release of serotonin from these cells is dysfunctional (Izzati-Zade, 2008).

The role of serotonin in the migraine process was strongly supported in positron emission tomography (PET) studies which indicated activation of the brain stem during migraine attacks, particularly in the dorsal raphe and the locus ceruleus areas (Boz et al., 2004; Di Piero et al., 2001; Park et al., 2006); serotonergic innervation in the central nervous system (CNS) is known to arise from these areas (Balaban, Jacob, & Furman, 2012; Hamel, 2007).

In addition, changes in the metabolism of 5-HT have been associated with the dynamics of migraine attacks (Hamel, 2007; Izzati-Zade, 2008; Panconesi, 2008; Schwedt, 2007). Between migraines, a low central 5-HT disposition has been recorded (Panconesi, 2008; Peterlin et al., 2009; Suprongsinchai, Storer, & Srikiatkachorn, 2014). Release of serotonin is then increased during the attack (Panconesi, 2008). These observations led to the initial suggestion of a biochemical theory involving serotonin in the pathogenesis of migraine

and, after further studies, to the formulation of the “serotonin hypothesis” (Izzati-Zade, 2008). As it is the result of several bodies of work, the “serotonin hypothesis” of migraine is a global term that incorporates several proposals of how serotonin is implicated in migraine. For example, two theories viewed serotonin release as the migraine attack trigger but differed on how serotonin was released (Davidoff, 2002).

In the study by Park et al. (2006), the possible relationship between two serotonin transporter protein polymorphisms, 5-HTTLPR and VNTR, and HA in patients with migraine without aura ($n = 97$, $M_{age} = 45.8$, $SD = 9.5$) and in controls ($n = 100$, $M_{age} = 48.3$, $SD = 9.0$) was investigated. The VNTR polymorphism showed genotypic differences in the migraine group compared to the control group. In this polymorphism two genotype frequencies were compared between the two groups and both were significantly higher in the migraine group ($p = .017$ and $p = .013$). It was hypothesized that these differences resulted in a reduced reuptake of serotonin, thus possibly influencing the serotonergic system and the development of migraine (Park et al., 2006) as the reuptake of serotonin by the serotonin transporter is crucial in maintaining 5-HT homeostasis (Hamel, 2007).

Hamel (2007) noted evidence indicating that migraine is consequential to a low 5-HT state although the steps between the two events are unknown. As noted above, depression is also associated with low serotonergic activity (Cahill & Murphy, 2004; Hamel, 2007; Robinson et al., 2010). This commonality is interesting as migraine and mood depression are often comorbid (Hamel, 2007; Hung, Liu, Fuh, Juang, & Wang, 2006; Punay & Couch, 2003; Torta & Ieraci, 2012) and some medications used to treat migraine are anti-depressants such as SSRIs (Schwedt, 2007). Therefore, it is suggested that migraine is associated with a low serotonin state.

3.6. Migraine and Harm Avoidance: Underpinned by the serotonergic system?

It is plausible that there is a system able to link personality, migraine, as well as anxiety and depression. Merikangas, Merikangas, et al. (1993) noted that the onset of anxiety, migraine, and depression appeared to occur sequentially and in this order. Based on these findings, Gentili et al. (2005) suggested that the chronological order could point towards a model. It was put forward that anxiety, through mental processes, in conjunction with molecular brain mechanisms, plays a role in the onset of primary headache. Primary headache would then be the catalyst in a psychoneurobiological cascade in the direction of a mood disorder such as depression. It was considered equally feasible that this order could be reversed and mental suffering could be a factor in somatic pain (Gentili et al., 2005).

With regards to personality, it has been proposed that migraine patients exhibit a specific personality profile (Gentili et al., 2005; Merikangas, Merikangas, et al., 1993; Merikangas, Stevens, et al., 1993; Pompili et al., 2010). Of the four temperament dimensions in Cloninger's theory, a higher score on Harm Avoidance (HA) in these patients is plausible in their personality profile. The serotonin neurotransmitter has been linked with migraine (Abbate-Daga et al., 2007; Sánchez-Román et al., 2007), HA (Gerra et al., 2000) and depression and anxiety. It is therefore possible that the serotonin neurotransmitter underlies both HA and migraine and may be a factor in their association. These potential relationships are depicted in Figure 3.2 and herewith discussed.

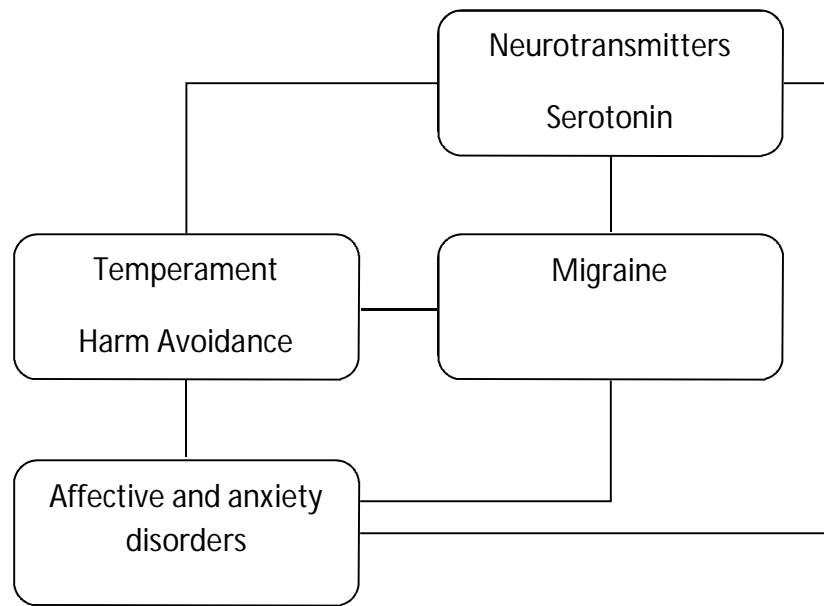


Figure 3.2. The serotonergic system underlying both HA and migraine.

As discussed in Chapter 2, perception of the pain associated with a migraine attack is a central factor in these relationships as the beliefs and feelings one has about pain can have physiological outcomes (Lake III, 2009). Affect (both temporary and more stable), cognition, and personality could influence pain perception in migraine and thereby related behaviours. This then becomes a self-enforcing cycle as the pain perception worsens the pain experience (Gustin et al., 2016). Examples of how this can occur with regards to mood and cognition are described in the article by Goli, Asghari, and Moradi (2014), hereunder discussed.

The results of the study by Goli et al. (2014) indicated that mood can alter the degree of pain reported by patients with migraine. Their final sample of 60 female migraine patients ($M_{age} = 34.52$, $SD = 9.75$) were randomly allocated into one of three mood induction conditions of equal size (20): Depressed group, control group, and elated group. Participants initially completed questionnaires including the BDI, the Pain Catastrophizing Scale (PCS), and the Pain Numerical Rating Scale (PNRS). Following completion of these questionnaires, the experiment was carried out over a series of four steps. The first step was to gather

baseline scores of cheerfulness, depression, and pain. At this point, nine participants ($N = 71$) were excluded as their baseline pain-rating scores were significantly different from the original sample ($N = 80$) so that homogeneity within the sample was not possible. The second step was a pain-provoking cognitive exhaustion task followed immediately by participants rating their pain. A further five participants ($N = 66$) were excluded as their pain increase was not large enough to meet the pre-determined change criterion. Thirdly, the participants underwent the mood induction task before again rating their cheerfulness, depression, and pain. Six participants ($N = 60$) were excluded at this juncture as their mood rating had not changed as compared to step 1 measures. In step 4, the final step, the participants again completed the cognitive exhaustion task before rating their pain. Results indicated a significant difference ($p = .048$) between the three groups in pain catastrophizing but no significant differences ($p = .18 - .88$) for age, pain duration, pain intensity, or depression. It was also indicated that mood state can change pain perception among patients with migraine. Depressed mood induction was related to an increase in pain ratings, an elated mood induction reduced these ratings, and there was no significant change within the control group (Goli et al., 2014). Goli et al. (2014) further note that the relationship between migraine and depression is most likely bidirectional. Depression worsens pain perception and may trigger headaches while migraine further depresses mood. Furthermore, cognitive factors can play a role in pain perception. Pain catastrophizing was a confounding variable in the mood-pain relationship and accounting for this variable reduced the effect of mood on pain intensity. This indicates that cognition is influenced in migraine and cognitive errors, such as catastrophizing, can have an impact on pain intensity (Goli et al., 2014). It has therefore been indicated that mood and affective state as well as cognition can play roles in migraine pain perception. However, the generalizability of these findings is limited to females and the exclusion of participants during the experiment reduces the effects of random allocation.

Central to this study, and as Bussone and Grazzi (2013) noted, personality has been related to migraine and may play a role in the perception of its pain as well. Temperament dimensions have been described as predictors for migraine and are heritable, as well as related to underlying neurobiological systems. HA in particular is associated with serotonin (Abbate-Daga et al., 2007). Schürks et al. (2011) note that serotonin metabolism and the processing of responses mediated by the serotonergic system are often described as altered in migraine patients. This would indicate that HA would be likely to be influenced in individuals suffering from this condition. Therefore it has been suggested that dysfunctions in serotonin activity mediate migraine as well as alterations in HA, as they both appear to be related to the serotonergic system.

This was investigated in the second aim of the study by Park et al. (2006), where the researchers postulated that HA would be higher in individuals suffering from migraine without aura due to their relationships with serotonin. As noted previously, this association was indeed present when comparing the migraine group ($n = 97$, $M_{age} = 45.8$, $SD = 9.5$) to the control group ($n = 100$, $M_{age} = 48.3$, $SD = 9.0$) as the former had significantly higher HA scores ($p < .001$). The migraine sample was then separated into two groups based on the VNTR polymorphism, which had revealed genotypic differences in the migraine group compared to the control group. However, following division, a significant difference in HA scores was not found. Thus, the results obtained from this study could not establish that HA was correlated with the VNTR polymorphism. The authors reasoned that migraine appeared to be linked to several genes, and HA may be the result of other genetic contributions (Park et al., 2006).

The results from Di Piero et al. (2001) indicated that both groups had greater HA scores than the reference values ($p < .001$). Due to the relationship between HA and serotonin this result supported the hypothesis that the serotonergic neurotransmitter system plays a role in the pathophysiology of both migraine and TTH. Between attacks it is reported that migraine patients show lower 5-HT and higher 5-hydroxy-indoleacetic acid (5-HIAA) plasma concentrations. However, during attacks the opposite is present in plasma concentrations. A decreased 5-HT platelet concentration is also reported during a migraine attack. Therefore, the authors concluded that this showed a high basal turnover rate for serotonin which was in keeping with the high HA scores reported by the migraine patients (Di Piero et al., 2001). However, a lower score in NS was also observed when comparing migraine patients to controls. As this temperament is related to the dopaminergic neurotransmitter system it also indicates that this system plays a role in the pathophysiology of migraine (Di Piero et al., 2001).

In contrast, Boz et al. (2004) did not find a significant difference in HA when comparing migraine patients and controls. This was not in accordance with their expectations given that serotonin has been implicated in both the development of migraine and HA. The authors advocated that this was due to differences in how serotonin is regulated in migraine and how it is regulated in HA scores (Boz et al., 2004).

It is therefore argued that the perception of migraine pain is influenced by mood and emotional state, pain cognitions, and personality. It is further advocated that this perception is influential in the behavioural reactions to and experience of that pain, thus resulting in a vicious cycle. The serotonergic system has been implicated as a role-player in the above factors, including both the temperament HA and migraine, and therefore could be

instrumental in these interactions. However, this is a complicated system, if indeed a system, and what first remains to be confirmed is the association between the HA temperament and migraine, and the association between the HA temperament and serum serotonin concentration.

3.7. Summary of chapter

A personality specific to migraine has long been a topic of interest and its history and implications were discussed in this chapter. Related to the previous chapter, it was argued that Cloninger's HA and its proposed neurotransmitter serotonin would be significantly associated with migraine as part of a comprehensive biopsychosocial system including personality and neurotransmitter systems. However, the literature reviewed in this chapter indicated conflicting results, both with regards to the relationship between temperament dimensions and neurotransmitter systems, as well as the expected correspondence between migraine and HA as a result of a shared mediation by the serotonergic system. The inconsistent findings therefore informed the aims of the study which, together with the method, are discussed in the next chapter.

CHAPTER 4: RESEARCH METHODOLOGY

This chapter serves to describe the research design of the study. This chapter introduces the objectives and hypotheses of the current study in detail as well as the paradigmatic approach taken throughout in order to understand the theoretical assumptions of the study. The key concepts and variables are described as well as the sampling and data collection method. The instruments utilised, both psychological and physiological, are explained and critiqued in detail. A summary of the quality assurance of the study is then given. The ethical concerns of the study are discussed as well as the funding and roles of the researcher in this study.

4.1. Aims and overview

There were two aims of the study. The first aim of this study was to investigate the relationship between the four temperament dimensions identified by Cloninger and serotonin neurotransmitter serum concentration in both migraine patients and controls. A second aim was to explore how temperament categories are distributed amongst MO sufferers. Both migraine patients and controls completed three questionnaires related to demographic factors, headache symptoms, and temperament. All participants donated a blood sample to assess serotonin concentrations levels, using a serotonin-specific enzyme-linked immunosorbent assay (ELISA). The data generated was used to accept or reject the null hypotheses. The objectives of the study were to determine the:

- Temperament trait distribution evinced by 43 MO sufferers and 23 age-matched healthy controls.
- Mean serotonin concentration indicated by each group.

- Relationship between each temperament dimension and serum serotonin in each group.

4.1.1. Research questions

The research questions were derived from the above aims and objectives:

1. Are there significant differences between the MO group and the control group in each of the measured dimensions of temperament?
2. Are there significant differences between the MO group and the control group in the level of serotonin concentration?
3. Is there a significant relationship between each of the measured dimensions of temperament and serotonin concentration?

4.1.2. Hypotheses

Three hypotheses were proposed for the study. These were:

Hypothesis 1:

$H_0 =$ There is no temperament profile associated with MO

$H_1 =$ A high mean HA score is associated with MO

$$p \leq .05$$

Hypothesis 2:

$H_0 =$ There is no correlation between MO and serum serotonin

$H_1 =$ There is a correlation between MO and serum serotonin concentration

$$p \leq .05$$

Hypothesis 3:

$H_0 =$ There is no covariance between temperament scores and serum serotonin

$H_1 =$ There is a covariance between HA and serum serotonin concentration

$$p \leq .05$$

4.2. Research paradigm

A paradigm is the worldview adopted by the researcher (Ponterotto, 2005; Racher & Robinson, 2002). Each paradigm has its own philosophical and conceptual assumptions about the world and how it can be studied (Ponterotto, 2005). The paradigm guides the choice of tools, instruments, participants, and method in order to remain philosophically consistent and true to the goals of the paradigm (Cooper, 1997; Ponterotto, 2005). The manner in which the paradigm guides the research process to the ultimate production of knowledge is indicated in Figure 4.1 (Adapted from Carter & Little, 2007). Each term is described below, but briefly, the paradigm determines the ontological perspective (What is reality?) and both guide the epistemological stance (What knowledge can we find out?). From these axioms, the methodology and methods which can be used in the study are decided. Each perspective is influenced by those which are prior in order to ensure consistency of the philosophical assumptions of the paradigm. It is necessary that each flows from the other otherwise the knowledge produced by the study is not in keeping with the view of reality and what we can learn about it, rendering it unusable.

The research paradigm adopted in this study is post-positivism. Post-positivism developed in response to the criticisms of two of positivisms' central tenets: naïve realism and dualism (Cooper, 1997; Ponterotto, 2005). Work within a post-positivist paradigm holds

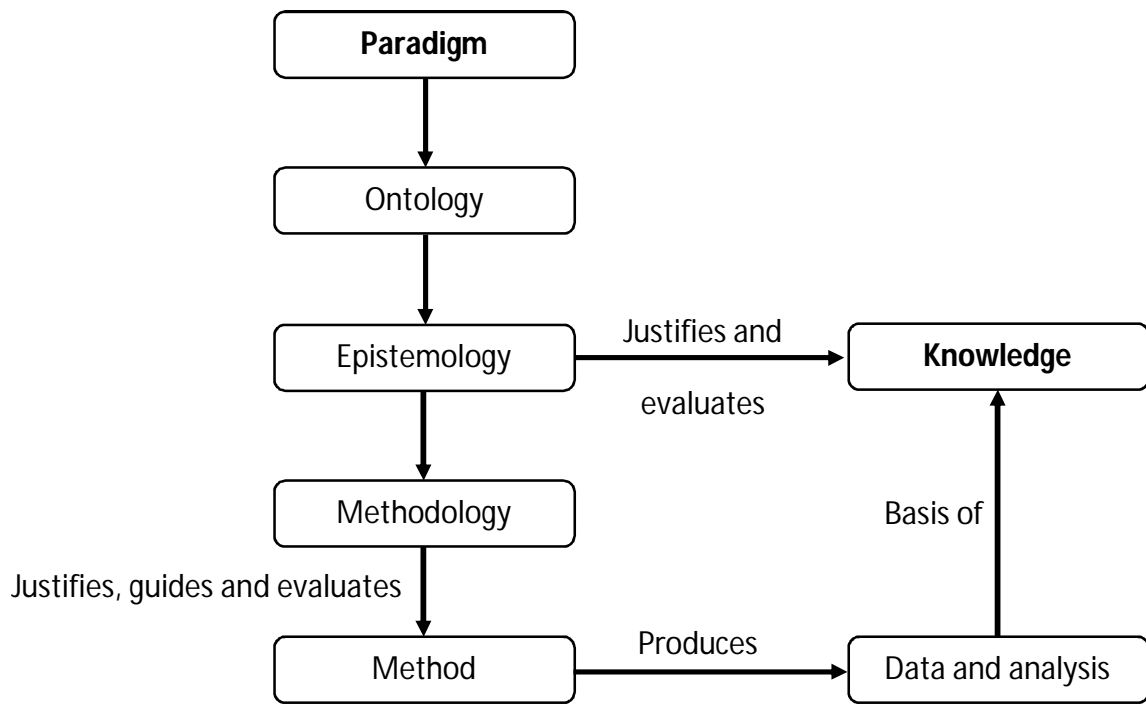


Figure 4.1. Process by which the adopted paradigm guides the research study (Adapted from Carter & Little, 2007).

that the research is influenced by several theories which are not absolute and are therefore subject to change if disproven (Mackenzie & Knipe, 2006). Although this study uses Cloninger’s theory, it is accepted that this theory is fallible. Therefore, it is equally feasible that the results would not support this theory as that they would align with it.

Researchers working within this paradigm can pursue research either qualitatively or quantitatively, but it most oft be aligned with quantitative methods of data collection and analysis (Mackenzie & Knipe, 2006). The research questions in this study involved identifying a correlation between two numerical values, indicating a quantitative approach. This paper is therefore a post-positivist quantitative correlational study.

4.2.1. Ontology

Ontology refers to the nature of reality and being. That is, ontology refers to how the paradigm perceives the form and nature of reality as well as what can be known about reality (Ponterotto, 2005). There are two ontological perspectives. The first takes the stance that there is one reality independent of human consciousness and experience. The second is that there are multiple realities which are constructed through our thoughts, dependent on human consciousness and experience (Levers, 2013).

In both positivism and post-positivism, there is one true reality. However, the naïve realism of positivism contends that this reality is able to be accurately measured (Ponterotto, 2005). In post-positivism, critical realism is adopted (Haverkamp & Young, 2007; Ponterotto, 2005). It is assumed that there is one reality, but it cannot be accessed completely and therefore can only be imperfectly measured (Haverkamp & Young, 2007; Levers, 2013; Ponterotto, 2005).

4.2.2. Epistemology

Epistemology relates to knowledge: its study, how it is acquired, and the relationship between the researcher and the research participant (Ponterotto, 2005). Post-positivism espouses that there is an absolute truth and there are etic (universal) laws (Levers, 2013). However, the objective reality cannot be fully captured as produced knowledge is influenced by contextual factors and therefore regarded as provisional (Cooper, 1997; Levers, 2013; Ponterotto, 2005). Research within the post-positivist framework aims for progression towards the truth and acknowledges that the produced knowledge is only part of the truth or an approximation (Levers, 2013).

However, post-positivists do attempt to produce knowledge that can be considered generalizable within a given context (Cooper, 1997; Ponterotto, 2005). One way in which they attempt to do so is to replicate results over similar situations by employing similar methods (Cooper, 1997). This study is attempting to replicate the finding that HA is correlated with the serotonin neurotransmitter. It is also attempting to replicate the finding that the HA temperament is higher in migraine patients than in controls.

Additionally, post-positivists include corrections within their method for individuality in order to make their samples and situations as representative as possible. Without these corrections, individuality of both the sample and the researcher is not taken into account and conflicts with the purpose of this research paradigm (Cooper, 1997). The current study employs rigorous, scientific methods which can be replicated.

Furthermore, the stance adopted by that of the researcher is one of objectivity so as to reduce the influence of the researcher on participants which could result in bias (Cooper, 1997; Ponterotto, 2005). The researcher in the present study was in direct contact with the participants during the recruitment stage. An objective stance was thus taken by the researcher, and each participant was treated professionally and equally.

4.2.3. Axiology

Axiology is the role and place of the values of the researcher in the research process. In the post-positivist paradigm, the values of the researcher are not afforded a role (Ponterotto, 2005) as they would be regarded as a source of bias (Haverkamp & Young, 2007). In order to take this into account, standardized and systematic methods were employed

in the current study. However, the choice of research topic is reflective of the values of the researcher (Ponterotto, 2005). The researcher in the current study acknowledges that there is bias in choosing a topic where an eventual aim is treatment of a serious disorder. Therefore, this was kept in mind during the research process in order to prevent influence of the researchers' values.

4.2.4. Methodology

Methodology is the analysis of the assumptions, principles and procedures of the methods used by the researcher in the research process (Schwandt, 2007). In post-positivism, a scientific methodology is followed. In this approach, methods are chosen which control and manipulate variables and which exclude the personal values of the researcher. The aim of implementing this position is to identify and explain relationships between variables which will lead to the development of etic laws, enabling the eventual prediction and control of phenomena. In order to do so, the methods employed by post-positivists are generally experimental and quasi-experimental (Ponterotto, 2005). In this research study, the methods used align with this approach.

4.3. Key concepts and variables

The temperament dimensions in this study were those put forth by Cloninger in his Psychobiological Theory of Personality: NS, HA, RD, and P. As noted in the previous chapter, temperament traits are considered to have a genetic basis, are exhibited in the early stages of development, and shape an individual's automatic responses to stimuli (Celikel et al., 2009). The temperament dimension of NS refers to a preference for the initiation of

behaviour whilst HA signifies bias towards termination of behaviour as the individual foresees a potential problem or punishment. RD describes the maintenance of the behaviour in the expectation of a social reward and lastly, P denotes the perseverance in the behaviour despite obstacles such as fatigue (Celikel et al., 2009; Conrad et al., 2007; Conrad, Wegener, Geiser, & Kleiman, 2013).

Serotonin (5-HT) is a neurotransmitter which is derived from the amino acid tryptophan (Berumen, Rodríguez, Miledi, & Garcia-ALcocer, 2012; Meyer, van Papendorp, Meij, & Viljoen, 2002; Nakamura & Wong-Lin, 2014). There are seven serotonin receptor families (5-HT1-7) which have been classified. With regards to brain anatomy, the cell bodies of serotonergic neurons are mostly found in the midline nuclei of the brain stem (Meyer et al., 2002). More specifically, in the raphe nuclei (Celada et al., 2013; Nakamura & Wong-Lin, 2014). These neurons project to the hypothalamus, limbic system, neocortex and the spinal cord. The functions of serotonin include a role in emotional changes and disturbances as well as body temperature regulation, inhibition of pain impulses in the spinal cord, circadian rhythm regulation, and slow-wave sleep initiation (Meyer et al., 2002).

4.4. Research design

Temperament and the serotonin neurotransmitter concentration could not be manipulated by the researcher and random assignment of the participants was not possible. Rather, this study was aimed at identifying whether or not there was a relationship between the two variables, both within the population of patients suffering from MO and a control group, and then making predictions from this information. The quantitative independent variable was serotonin neurotransmitter concentration and the quantitative dependent variable

was temperament dimensions. Therefore, this is a non-experimental quantitative correlational research design (Johnson, 2001).

4.5. Population and sample

The population identified in this study was MO patients. This is defined as a recurrent headache disorder in which the attacks last between 4 and 72 hours. The third edition of diagnostic criteria, as listed by the International Classification of Headache Disorders (ICHD), is as follows:

Table 4.1.

International Headache Society diagnostic criteria for migraine without aura

- A. At least 5 attacks fulfilling criteria B–D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
 - a. Unilateral location
 - b. Pulsating quality
 - c. Moderate or severe pain intensity
 - d. Aggravation by or causing avoidance of routine physical activity
- D. During headache at least one of the following:
 - a. Nausea and/or vomiting
 - b. Photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis

Headache Classification Committee of the International Headache Society (IHS) (2013)

The previous classification, ICHD-II, differed on item E which stated “Not attributed to another disorder” (Headache Classification Committee of the International Headache Society (IHS), n.d.).

Individuals who meet all criteria except at least five attacks are coded as Probable migraine without aura (PMO) (Headache Classification Committee of the International

Headache Society (IHS), 2013). In addition, the design of the study is such that a full physical screening was not performed and therefore the researcher cannot rule out all other ICHD-3 diagnoses. Participants who are better classified as having Probable migraine without aura (PO) were included in the MO group. The criteria for PMO according to the International Classification of Headache Disorders (ICHD) states A) Attacks fulfilling all but one of criteria A-D for migraine without aura (MO), and B) Not attributed to another disorder.

Individuals were recruited from the Gauteng province using advertisements and snowball sampling. Individuals between the ages of 18 and 65 years were recruited between May 2014 and January 2016. Therefore the inclusion criteria were between the ages of 18 and 65 years, a Gauteng resident, and legally an adult.

Exclusion criteria were selected based on previous literature, as indicated below, as well as the guidelines for good practice in health research. In order to protect participants who are considered vulnerable (Department of Health, 2006), participants either pregnant or lactating, as well as participants diagnosed with a bleeding or clotting disease or a terminal or degenerative disease were excluded. Volunteers who indicated psychoactive drug usage were excluded from the study because the use of these drugs can change serotonergic activity (Peirson et al., 1999).

In addition to the two main subtypes of migraine (MO and MA) and PMO, there are also migraine-related conditions which may or may not include headache as a symptom. The medical diagnosis of all three of these subtypes are made without knowing aetiology (Gupta, Gupta, & Borad, 2016). Participants were therefore excluded on the basis of a previous

diagnosis which literature indicates could be a differential diagnosis for MO and therefore a confounding factor. Differential diagnoses include seizure and stroke which may also be the cause of the migraine subtype itself (Gupta et al., 2016). Hofstra, Hageman, and de Weerd (2015) found in their study using both children ($n = 29$, $M_{age} = 10.9$) and adults ($n = 226$, $M_{age} = 40.7$) suffering from epilepsy, that significantly more patients have comorbid migraines ($p < .001$) than individuals without epilepsy. There are four variants of the association between migraine and epilepsy. In addition, two of the four relationships are complex and involve controversial terminology, diagnosis, and classification debates (e.g. “Migralepsy”) (Cianchetti, Pruna, & Ledda, 2013). This complicates data analysis unnecessarily. With regards to stroke, a higher incidence of vascular disease (VD) has been reported in migraineurs (Sacco, Ricci, Degan, & Carolei, 2012). However, the systemic vascular vulnerability associated with migraine which would explain this increased risk of VD is not yet fully understood (Sacco et al., 2012; Schürks et al., 2010). Therefore, participants who had experienced either a seizure event or a stroke were excluded to minimise confounding variables. Hypertension is a further comorbid condition (Wang, Chen, & Fuh, 2010) and participants who indicated this condition were excluded.

The hormonal changes accompanying both the onset of the perimenopausal period and menopause can improve or worsen a pre-existing migraine condition or leave it unchanged (Ibrahimi, Couturier, & MaassenVanDenBrink, 2014; Sacco et al., 2012). Therefore, menopause was also an exclusion criterion.

4.6. Data collection methods and fieldwork practice

The current study is linked to an ongoing, larger project and therefore data collection and fieldwork ran concurrently. The larger study examined the biopsychosocial correlates of PMO and participants were asked to complete a biographical questionnaire, a researcher-designed headache questionnaire, and the Tridimensional Personality Questionnaire (TPQ) online through Qualtrics, a suite of survey software accessible on the web (<https://www.qualtrics.com/>). Participants were also asked to submit a blood sample after having fasted for 10 to 12 hours to the closest Ampath laboratory or to one of the five depots in Pretoria and Johannesburg, Gauteng, during a specific time window (08:00-10:00).

Data was collected over the period of two years. Blood samples from all participants were drawn by Ampath and stored by the researcher at the appropriate temperature. They were later analysed by the researcher under supervision¹. Analysis was conducted in the laboratory at the University of Pretoria Prinshof campus under supervision.

4.7. Questionnaires

4.7.1. Biographical and researcher-designed headache questionnaires

The biographical questionnaire was designed to capture basic data about respondents' gender, age, education level, home language, ethnicity, relationship status, employment status, eating habits, exercise habits, height, and weight.

¹ Both Ms Catherine Govender and Dr Alida Koorts acted as supervisors.

The researcher-designed headache questionnaire had 12 items regarding headache duration, pain severity, as well as pain location, triggers and treatments and medication. This questionnaire was designed based on literature and clinical headache reporting questionnaires (Breslau & Davis, 1993; Headache Classification Committee of the International Headache Society (IHS), 2013). It is included in Appendix 1.

4.7.2. The Tridimensional Personality Questionnaire

The TPQ is designed to assess the three temperament dimensions initially described by Cloninger, NS, HA, and RD, and is a 100-item self-report true or false personality inventory (Cloninger et al., 1991; Giancola et al., 1994; Nyman et al., 2009; Strakowski et al., 1993). The temperament dimensions are associated with dopaminergic, serotonergic, noradrenergic activity respectively (D'Agostino, Francia, Licursi, & Cerbo, 2010; Villani et al., 2010). As explained below, the scale also measures P which is associated with glutaminergic activity (Villani et al., 2010).

The TPQ originally assessed twelve subdimensions, four for each of the original three temperament dimensions (NS, HA, and RD). However, the RD trait is now scored over three of its four subdimensions: Sentimentality versus insensitiveness (RD1), Attachment versus detachment (RD3), and dependence versus independence (RD4). The second subdimension, persistence versus irresoluteness (RD2), is scored as a separate primary temperament dimension termed Persistence (P) (Stallings et al., 1996). This is due to the fact that the RD2 subdimension reflects the P dimension rather than RD (Miettunen, Kantojärvi, Veijola, Järvelin, & Joukamaa, 2006). NS was scored using all four of its subdimensions: Exploratory excitability versus stoic rigidity (NS1), impulsiveness versus reflection (NS2), extravagance

versus reserve (NS3), and disorderliness versus regimentation (NS4). HA was also scored as the sum of its subdimensions: Anticipatory worry versus uninhibited optimism (HA1), fear of uncertainty versus confidence (HA2), shyness with strangers versus gregariousness (HA3), and fatigability and asthenia versus vigour (HA4) (Stallings et al., 1996). Table 4.2 describes the temperaments, their subdimensions, examples of items found within the subdimension, and the neurotransmitter hypothesized to underpin the respective temperament dimension (Adapted from Cloninger et al., 1991; Stallings et al., 1996; Tuominen, 2014; Villani et al., 2010).

4.7.2.1. Psychometric properties of the Tridimensional Personality Questionnaire

It should be noted that Cloninger's original theory, which the TPQ was developed to assess, is now a model for the temperament traits of personality as it does not assess the added character dimensions (Stallings et al., 1996). The psychometric validity of the TPQ has been supported in previous studies (Bagby, Parker, & Joffe, 1992; Giancola et al., 1994; Miettunen et al., 2006; Nixon & Parsons, 1989; Otter, Huber, & Bonner, 1995; Sher, Wood, Crews, & Vandiver, 1995; Stallings et al., 1996) although it must be noted that the validity of the RD and P scales is weaker (Miettunen et al., 2006; Otter et al., 1995). As discussed later, this may be due to the TPQ initially only measuring three temperament dimensions before the addition of the P dimension.

Other studies investigating the psychometric properties of the TPQ evaluated only the initial three dimensions. Construct validity is particularly important for instruments attempting to measure personality dimensions (Nixon & Parsons, 1989). Nixon and Parsons (1989) conducted a study on 225 male and female college students to assess the validity of

Table 4.2.

Temperament dimensions, their subdimensions, examples of items in each dimension, and the hypothesized neurotransmitter associated with each dimension

Temperament	Subdimensions	Examples of Items	Neurotransmitter
Novelty Seeking	NS1: Exploratory excitability vs stoic rigidity (9 items) NS2: Impulsiveness vs reflection (8 items) NS3: Extravagance vs reserve (7 items) NS4: Disorderliness vs regimentation (10 items)	I do things spontaneously	Dopamine
Harm Avoidance	HA1: Worry and pessimism vs optimism (10 items) HA2: Fear of uncertainty vs confidence (7 items) HA3: Shyness with strangers vs gregariousness (7 items) HA4: Fatigability and asthenia vs vigor (10 items)	I get tense and worried in unfamiliar situations	Serotonin
Reward Dependence	RD1: Sentimentality vs insensitiveness (5 items) RD3: Attachment vs detachment (11 items) RD4: Dependence vs independence (5 items)	I'm strongly moved by sentimental appeals	Noradrenaline
Persistence	RD2: Persistence vs irresoluteness (9 items)	I work long after others give up	Glutamate

the TPQ. Their results also provided support for the construct validity of the three temperament dimensions. Their results further indicated that female subjects scored higher on the HA and RD dimensions (Nixon & Parsons, 1989). These findings were likewise found in the study performed by Otter et al. (1995). Both authors reported that this similarity in results provided additional construct validity for both HA and RD (Nixon & Parsons, 1989; Otter et al., 1995).

However, other studies proposed four rather than three temperament dimensions. Support for the structural and external validity of the TPQ was reported by Waller, Lilienfeld, Tellegen, and Lykken (1991), whose participants were adult twins and twin family members. Preliminary support for the convergent and discriminant validity of HA and NS was found as the subdimensions of each scale correlated more with each other than with the scales designed to assess the other dimensions. However, this was not true for the RD dimension as its subdimensions RD1 (sentimentality vs insensitiveness) and RD2 (persistence vs irresoluteness) were not significantly correlated ($r = .047$). This was proposed as a possible reason for the lower internal consistency of the RD scale ($\alpha = .72$) than both the HA and NS dimensions as well as the RD1 subdimension ($\alpha = .75$). This raised the question of whether the RD1 and RD2 subdimensions do in fact measure the same construct. A further factor analysis of the TPQ indicated that the loadings of the subdimensions better supported a four-factor rather than a three-factor model, with HA and NS more clearly defined. This is in accordance with the lack of shared variance of the two subdimensions of RD and it was concluded that they do not in fact measure the same construct (Waller et al., 1991).

Further studies corroborated with the aforementioned low validity of the RD dimension and proposed that there should be four dimensions. Giancola et al. (1994)

performed a study using 807 undergraduate students. They noted that although HA and NS appeared to have a fair degree of construct validity, the P dimension required further revision (Giancola et al., 1994). Miettunen et al. (2004) also reported that their psychometric study of the TPQ provided support for the internal consistency of the HA ($\alpha = .85$) and NS ($\alpha = .74$) dimensions but that RD ($\alpha = .61$) should be split into two parts. Even when they are separated, as in the TCI, the internal consistency of both RD ($\alpha = .69$) and P ($\alpha = .55$) are lower than the other two dimensions, NS ($\alpha = .78$) and HA ($\alpha = .85$) (Miettunen et al., 2004, 2007). In addition, it was reported that gender has an influence on the temperament dimensions and in turn is also influenced by age and cultural factors (Miettunen et al., 2007). The influence of culture was also reported by Otter et al., (1995).

Other studies have not provided support for the TPQ due to several psychometric limitations (Farmer & Goldberg, 2008a). Stewart, Ebmeier, and Deary (2004) conducted a reliability and validity assessment of the TPQ in a British sample of university students. Although the internal consistency of the total scales of HA, NS, and RD ranged from 0.72 to 0.90 and were all within the satisfactory range, the subdimension reliability coefficients for both NS, ranging between less than 0.60 and 0.70, and RD, ranging between 0.39 and 0.76, were poor. This indicates that they are weakly supported. HA showed the highest reliability coefficients for both the total scale ($\alpha_{\text{male}} = .90$ and $\alpha_{\text{female}} = .89$) = and its subdimensions (range between 0.72 and 0.90) (Stewart et al., 2004). The review by Carver and Miller (2006) reiterate the lack of a theoretical factor structure and the claim that several concepts are blended within scales. For example, the authors claimed that HA and NS both correlated with impulsivity as measured by other personality inventories. With regards to serotonin and personality, the authors suggested that, rather than anxiety, serotonin was related to impulsiveness, aggression, and volatility (Carver & Miller, 2006). However, of the studies

that reviewed the majority had psychiatric (Borderline Personality Disorder patients or aggression patients) or non-clinical participants. No studies using a population suffering from chronic pain were included in their review. There may thus be some bias in their conclusions which casts doubt on the validity of their suggestion.

Reliability and validity studies have not been performed for the South African population and therefore normative data from the Cloninger's studies using an American population were used. However, a study comparing the international temperaments as measured by either the TPQ or the TCI was performed by Miettunen et al., (2006), which supported the cross-cultural use of both tests.

4.8. Enzyme-Linked Immunosorbent Assay

A 5-ml blood sample was drawn from each participant using venepuncture (Peirson et al., 1999) during a specific time window (08:00-10:00) and the serum of each participant tested for the serotonin neurotransmitter concentration using ELISA. The materials used as well as their source and final amount are presented in Table 4.3. The range of the kit used is 5 ng/mL - 100 ng/mL and its sensitivity is 0.293 ng/mL (Abcam, 2015a, 2015b).

Briefly, ELISA is an immunoassay method which uses antibodies to capture an antigen, and subsequently an enzyme-labelled antibody to estimate the amount of captured antigen (Gan & Patel, 2013; Wakabayashi, 2010). A substrate which produces a colour change for the enzyme is used. A visible colour change indicates the presence of antigen (Gan & Patel, 2013).

Table 4.3

ELISA materials, source, and final amount

Material	Source	Final amount
Goat anti-Rabbit IgG Microtiter Plate	Abcam	96 wells
Serotonin Alkaline Phosphatase Conjugate	Abcam	2 × 150 ng
Serotonin antibody	Abcam	2 vials
Assay buffer	Abcam	27 mL
20 × Wash Buffer Concentrate	Abcam	27 mL
Serotonin standard	Abcam	2 × 250 ng
pNpp substrate	Abcam	20 mL
Stop solution	Abcam	5 mL

Competitive direct ELISAs were performed. This type of ELISA measures substance concentration by how much the substance interferes with an established pre-titrated system, i.e. the target antigen, serotonin, will compete with the system antigen for labelled antibodies. The higher the amount of target antigen, the fewer labelled antibodies will bind with the system antigen. This is then measured as a decrease in the expected optical density (colour). However, if there is no antigen in the participant sample, or the antigen is not similar enough to the system antigen, the competition will be limited and the expected colour will be unaffected (Crowther, 2001). A spectrophotometer was used to measure optical density (OD) in order to quantify the concentration of serotonin neurotransmitter in serum samples from the participants.

For the current study, a brief overview of the laboratory steps is herewith given. A goat anti-rabbit IgG antibody was precoated into each well on the Microtiter plate by the supplier. The researcher then added the standards and test samples to the wells along with an alkaline phosphatase (AP) conjugated serotonin antigen and a polyclonal rabbit antibody specific to serotonin (Abcam, 2015a, 2015b). At this point, the serotonin in the sample competes with the system antigen, illustrated in Figure 4.2 below.

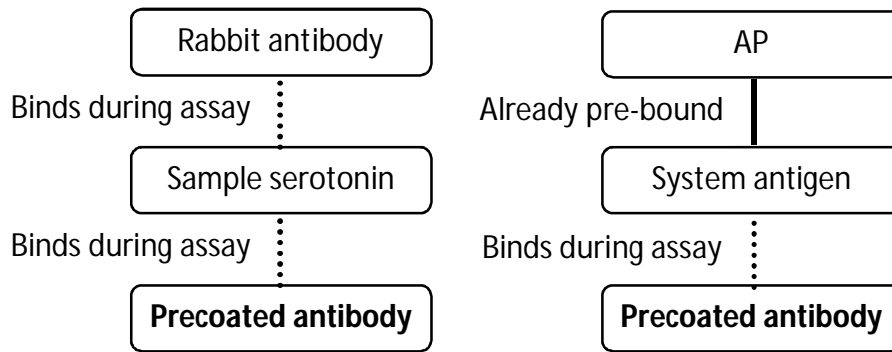


Figure 4.2: Competition between sample and system antigens during ELISA

Following incubation the excess reagents were washed away (Abcam, 2015a, 2015b). *p*-nitrophenyl phosphate (*p*Npp) substrate was then added which reacts with the AP enzyme to produce a yellow-coloured product (Abcam, 2015a, 2015b; SeraCare Life Sciences & Kirkegaard & Perry Lab Inc, 2013). Following incubation the enzyme reaction is stopped and the yellow colour generated is read at 405nm. The intensity of the yellow colouration is inversely proportional to the amount of serotonin captured in each well (Abcam, 2015a, 2015b).

4.8.1. ELISA laboratory protocol

Each microtiter plate has 96 wells. Twelve wells were set aside to calculate the standard curve. Thirty-eight participant samples were run on the first assay in duplicate. The participant samples were added in the random order they were collected, rather than being grouped as either migraine or control. They were performed in duplicate so as to assess within-plate variation (this will be discussed below in data analysis). This duplication is in accordance with the recommendation by Abcam (2015a, 2015b) to duplicate each sample for statistical reasons. This plate configuration is shown in Figure 4.3 with wells for calculating

the standard curve (S1-S6) and participant sample wells (U1-U38). The above well composition was also used for the second plate but using the remaining 28 participant samples (in duplicate).

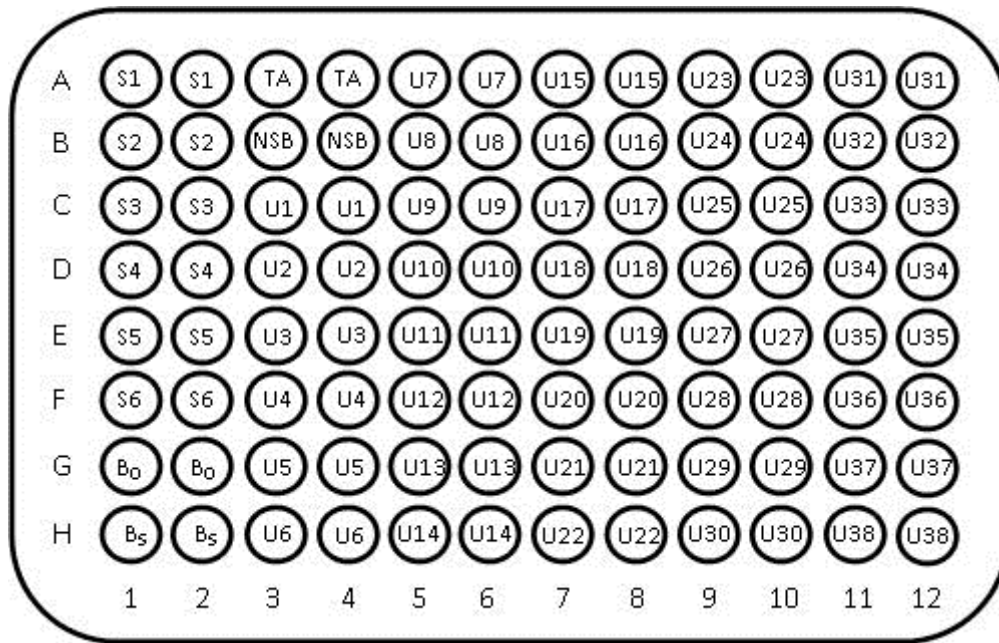


Figure 4.3. The first Microtiter plate configuration; each row is labelled (A to H) as well as each column (1 to 12) enabling the researcher to refer specifically to a well (e.g. G7).

In addition to the standard curve and sample wells, two wells were designated each for B₀ (0 pg/mL standard), blanks (B₅), total activity (TA), and non-specific binding (NSB). These wells refer to the controls which are used to assess the validity of the assay. The B₀ wells have no test serotonin added and therefore should evince the highest colour as no competition has taken place (positive control). Blanks are used to determine the background absorbance, which refers to any variation or contribution of the plate itself, which is then subtracted from all the other wells. No test or system serotonin should be identified in these wells. The values for these two wells should be low, approaching zero (negative control) (Abcam, 2015a, 2015b; Drummond, n.d.). The TA wells are a positive control used to ensure

that the enzyme is active (Cayman Chemical, 2016). The NSB wells allow the researcher to check if the labelled antibody is contributing to the overall absorbance by binding non-specifically to the well. These two wells should give values slightly higher than the blank wells (Drummond, n.d.). This is a negative control used to check for false positives (Sino Biological Inc, 2016).

The protocol as given in the Abcam instructions for use when performing the analysis for serum was followed (Abcam, 2015a). However, the manual recommends that the participant sample is diluted in a 1:16 ratio. Using this recommendation, the first ELISA was run. Absorbance was read at 405nm with a correction of 570nm. However, the resulting OD values were much higher than those generated by the standard curve, i.e. the colour was very strong indicating little to no serotonin in the sample. These results were unusable as the curve could not be used to calculate the serotonin concentration. The second ELISA was run the following week but used dilutions of 1:2.5, 1:3, and 1:4. However, despite this correction the values were still much higher than the highest value on the standard curve. The manufacturers were therefore contacted who recommended that the sample not be diluted. Replacement kits were ordered, one provided by the manufacturers and one by the researcher, and the experiments run again without diluting the sample.

The use of the first plate was split over two sessions. In the first, the standards, blanks, NSB, and TA wells were used with four samples (1, 2, 8, and 10). This smaller experiment was run in order to ascertain whether the undiluted samples would render absorbance values that could be read on the standard curve. However, each “strip” (e.g. wells A1-H1) can only be used in its entirety and therefore four wells of this plate were not used in any of the

experiments. This initial experiment was successful. Therefore, fresh standards, B₀, Blank, NSB, and TA wells were run with 19 samples.

The second plate had to accommodate the remaining 15 samples which were not placed on the first plate as well as the remaining 28 samples. Only 38 samples could be run in duplicate on the second plate and therefore ten samples were run singly. These samples were selected using the Excel RAND function to create a randomised list from which the first ten samples were taken. Due to the lack of available wells, samples from the first plate could not be run again on the second plate for the purposes of calculating between-plate reliability. Both these points are therefore noted later as limitations of the study.

The absorbance was again read at 405nm with a correction of 570nm. The concentration of serotonin was determined by comparison to the standard curve using the calculations indicated in the manual provided by Abcam (Abcam, 2015a). The data analysis steps followed for the ELISA results are discussed in the data analysis section so as to group all data analysis undertaken in this study. The following section discusses the steps taken for quality assurance of the ELISA procedure.

4.8.2. ELISA precision assessment

The pros of using this method is that crude or impure samples can be used and have high reproducibility. In order to assess sensitivity and specificity and for quality control, the current study assessed the precision of the assay using the coefficient of variation (CV). The CV is the ratio of the standard deviation to the mean (Abcam, n.d.; Hanneman, Cox, Green, & Kang, 2011; SeraCare Life Sciences & Kirkegaard & Perry Lab Inc, 2013; Sino Biological Inc, 2016):

$$CV (\%) = SD/mean \times 100$$

CV is expressed as a percentage of variance to the mean; the larger the CV, the greater the inconsistency and inaccuracy of the results (Abcam, n.d.; Hanneman et al., 2011). This variation can result from a number of reasons during the experimental procedure (Table 4.4) and it is therefore important to follow the protocol carefully (Abcam, n.d.).

Table 4.4.

Factors which could influence the accuracy of the assay

Factor	Examples
Equipment	Calibration Maintenance Incubation temperature Laboratory temperature
Reagents	Shelf-life Contamination Initial purity Concentration
Samples	Blood factors Test temperature Storage conditions Blood/ serum Age
Plates	Antigen coverage Antigen consistency Antigen amount
Procedures	Reaction time Reagent measurement Incubation time Plate washing Sample measurement

Adapted from Gentleman, Hamada, Matthews, and Wilson, 1994.

The %CV for each sample was calculated by taking the SD of its duplicates, divided by the duplicate mean, and multiplied by 100. The within-plate, or intra-assay, CV was then

determined as the average of the individual CVs. Precision was assessed by comparison to the figures given in the Abcam instruction manual, presented below in Table 4.5, for low serotonin concentration (Abcam, 2015a). Usually, the between-plate CV is also calculated to assess reproducibility but this was not possible. The results of these calculations are given in Chapter 5: Results (section 5.4).

Table 4.5.

Precision of assay indicated by percentage CV

Precision	Serotonin (ng/mL)	Intra-assay %CV
Low	13.5	11.0
Medium	53.8	5.8
High	346.1	4.2

Adapted from Abcam (2015a).

4.9. Data management

Data from completion of the online questionnaires was automatically captured through Qualtrics and downloaded in the form of an MS Excel spreadsheet. All documents pertaining to the study (i.e. ethical clearances, informed consent forms, information brochures and leaflets, datasheets) were saved on password-protected computers only accessible by the researcher and supervisor. Blood samples were collected by a registered nurse at the Ampath laboratory and then transported to the storage freezer, in the locked laboratory, at the University of Pretoria Prinshof campus before the ELISA analysis was performed by the researcher under supervision. All unused blood samples were destroyed in accordance with correct laboratory procedure. In order to prevent repetition, the reader is referred to the ethical considerations section for additional information regarding data management (section 4.12).

4.10. Data analysis strategy

The current study made use of both descriptive and inferential statistical techniques during data analysis. Frequency analyses, χ^2 tests, Fisher's Exact tests, and the Mann-Whitney U-test were employed to give an accurate sociodemographic picture of the two groups and assess for significant differences on these variables. Spearman's Rho correlation coefficients were performed to check for a possible relationship between HA and serum serotonin concentration as well as for relationships between the temperament dimensions and subdimensions. Either the independent samples *t* test or the Mann-Whitney U-test was conducted to check for a relationship between migraine and the temperament score distribution as well as with serum serotonin concentration. Data was analysed using SPSS, version 23.0.

4.11. Quality assurance

With regards to the TPQ, the cross-cultural use of the test has been supported (Miettunen et al., 2006). This was taken into consideration when selecting a test appropriate for the current study, as care was taken to select a test that would be most likely to suit the South African context as no normative studies using this questionnaire have been performed in this country.

The ELISA method is a well-known (Lequin, 2005) and often used technique to determine serotonin concentration in human serum (e.g. Palus et al., 2015; Wipfli, Landers, Nagoshi, & Ringenbach, 2011). Laboratory procedures were undertaken with the utmost care in order to reduce sources of error and quality checks have also been introduced. However,

10 of the samples could not be run in duplicate. Therefore, for these 10 samples the CV could not be calculated and thus neither their validity, reproducibility, nor precision. To limit this shortcoming, these samples were chosen at random. In addition, due to complications encountered during the laboratory procedure, the between-plate analysis could not be achieved.

Lastly, both positive and negative controls were included on each of the ELISA plates for quality assurance of the assays. The B₀, NSB, and B_S controls performed as expected and supported the quality of assays. However, the TA wells are expected to render the highest OD values as they represent the total activity which was not the case in any of the three ELISAs. Therefore, an inquiry was sent to Abcam who contacted their laboratory to determine if similar values for the TA wells had been achieved in other tests (Abcam, personal communication, April 11, 2016). As the protocol had been followed correctly in its entirety they were unable to explain the value for the TA wells (Abcam, personal communication, April 19, 2016).

All other shortcomings and sources of error have been acknowledged and will be taken into account during analysis, interpretation, and discussion of the results. Where possible, steps have been taken to minimize the possibility of induced error or variation.

4.12. Ethical considerations and human subjects

Prior to the start of the study, approval was obtained from the Ethics Committee of the Department of Psychology at the University of South Africa. The guidelines described by the Council for International Organizations of Medical Sciences (CIOMS) and the World Health

Organization (WHO) were used to inform this study and are underpinned by general ethical principles, ethics related specifically to biomedical research, the Universal Declaration of Human Rights, the International Covenant on Civil and Political Rights, and the International Covenant on Economic, Social and Culture Rights, and human rights law underpin these guidelines (Council for International Organizations of Medical Sciences (CIOMS) & World Health Organization (WHO), 2002). These were followed during the development of the research proposal, developing and administering the informed consent procedures, during conduction of the study and will also direct future research outputs.

Informed consent was comprehensive and the following nine key points were made clear to the participants regarding their participation: A) **Respect for persons**; 1) All participants were legally adults; 2) Participation was voluntary for both components of the study, namely completion of the online questionnaire and blood donation; 3) The participants were also able to choose to participate in each component separately so that participation in one was unaffected by the other; 4) It was also stated that the participants were free to withdraw from the study at any point in time. This was particularly important as individuals may have doubts regarding blood donation at a later stage in the study; B) **Beneficence**; 5) Informed consent was also clear regarding the purposes and procedures of the study which are in keeping with good practice guidelines. For the blood sampling, it was stated that a trained professional from Ampath would be drawing the blood sample. The blood sample also required that certain conditions be met, such as the participant fasting for 8-10 hours before the blood sample was drawn, and therefore it was vital that these were clearly presented in the informed consent. Furthermore, the tests performed on each blood sample were specified as well as stipulating that any remaining blood sample was destroyed; 6) Possible risks involved were outlined as well. These risks include discomfort, bruising,

dizziness, or faintness. The use of trained professionals as well as the reassurance of being able to withdraw from the study at any point was designed to minimize these risks; 7) No cost would be incurred to the participant or their medical aid with regard to blood donation; 8) It was also noted that there was no incentive provided for participation in the study; and C) **Justice**; 9) All participants were able to take part in either and/or both parts of the study, no preferential treatment was given, and there was no prejudice if a participant chose not to take part. Informed consent also listed the researchers' contact details should the participants have had any questions or concerns.

All information regarding participant test results or health status was kept confidential. However, it was also stated in the informed consent that there were two exceptions. The first was a potentially serious problem indicated by their laboratory results, which was communicated to them by their general practitioner (details were requested in the online questionnaire). The second was requirement by law, such as in the case of a communicable disease, and the participant was informed of this in writing.

With regards to confidentiality, each participant name was automatically assigned a unique code. The online questionnaires were only accessible to the supervisor of this study as well as the administrator of Qualtrics, the online website used to design the questionnaire and capture responses, who had access to this online data and therefore signed a confidentiality contract. The researcher had access to the data after the participants' names had been replaced with their assigned code in the form on a MS Excel datasheet.

Publications or other scientific output will not use participant names or any other identifying factors. In addition, all information will be aggregated when analysed and therefore no participant will be reported on individually.

4.13. Funding and roles

This research was funded by the National Research Foundation (NRF). The NRF awarded Grantholder-Linked Student Support as this study is part of the larger PhD project by Ms Catherine Govender. This study was also funded by a Master's by Research and Doctoral Bursary from the University of South Africa (UNISA).

The questionnaires were entered into the online programme, Qualtrics, by Ms Govender. The Ampath laboratories were responsible for the blood sampling. The roles of the researcher included recruitment of participants, conducting the ELISA analysis as well as data capturing and analysis. ELISA protocols were supervised by Dr Alida Koorts at the Department of Physiology, University of Pretoria.

4.14. Summary of chapter

Chapter 4 described the paradigm, research design, population, and sample used for this study. This study was a non-experimental quantitative correlation study using a post-positivist paradigm. The population group was MO patients and a sample of 43 patients (male = 4, female = 39, $M_{age} = 36.6$, $SD = 11.2$) and 23 controls (male = 5, female = 18, $M_{age} = 28.8$, $SD = 11.5$) was used. A detailed description of all instruments used and the procedure followed for data gathering and the data analysis strategy was provided as well as quality

assurance, ethical concerns, and funding and roles. In the next chapter, the aims and researcher questions are reiterated followed by a detailed data analysis plan. Thereafter, each step taken during statistical analysis and the results of the study are detailed.

CHAPTER 5: RESULTS

The results of the study are presented in this chapter which begins with a brief overview of the aims and research questions which were presented in detail in chapter 4. Thereafter the detailed data analysis plan is presented followed by the results.

5.1. Aims and questions reiterated

The first aim of the study was to ascertain the relationship between the four temperament dimensions as delineated in Cloninger's personality theory and serum serotonin concentration. In the second aim of the study, the possibility of a specific migraine temperament profile was explored. The research questions that were therefore asked stated:

1. Are there significant differences between the MO group and the control group in each of the measured dimensions of temperament?
2. Are there significant differences between the MO group and the control group in the level of serotonin concentration?
3. Is there a significant relationship between each of the measured dimensions of temperament and serotonin concentration?

5.2. Data analysis plan

All of the statistical analyses were performed using SPSS for Windows, version 23.0. The level of significance for the study was set at 0.05. The final sample was comprised of 43 migraine participants ($n = 43$; 65.2%) as well as 23 control participants ($n = 23$; 34.8%). A diagram indicating the total number of respondents and the reasons for which others were

excluded is presented in Figure 5.1. As this study was part of a larger research project, 324 online questionnaires were completed. Thereafter, some participants ($n = 258$) were excluded based on criteria or lack of response. Two participants reported being diagnosed with a terminal illness and six other participants reported a degenerative nervous disorder and therefore these eight participants were excluded.

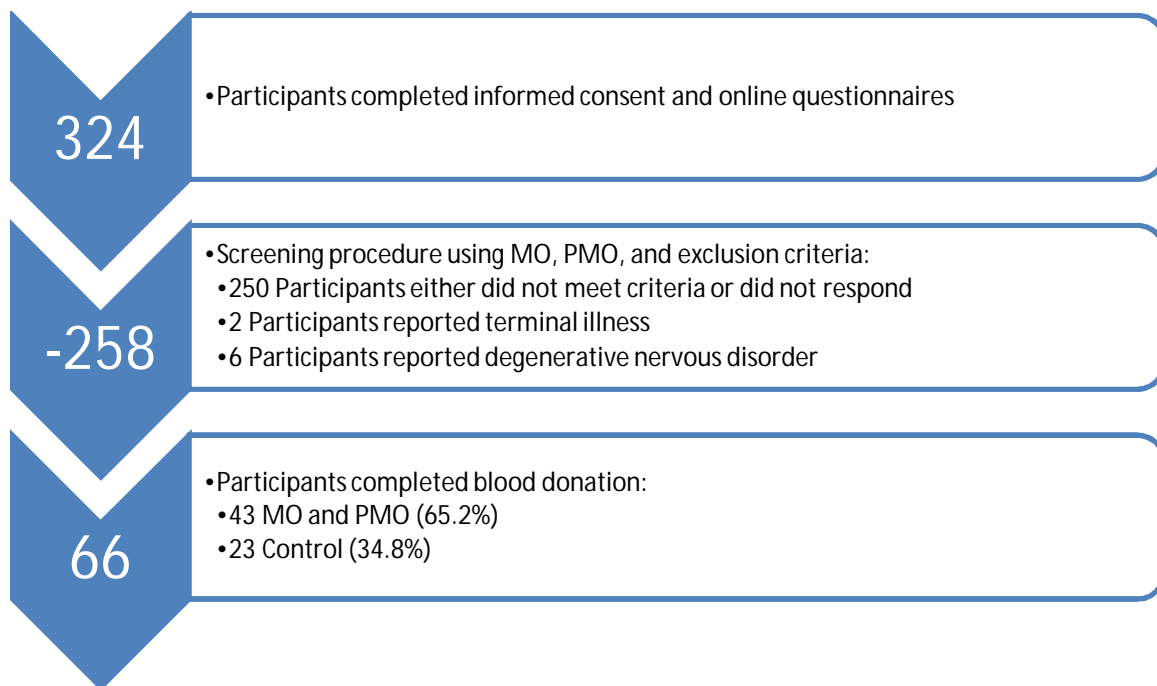


Figure 5.1. Flow chart of data collection.

The data analysis steps taken are now explained. Using only the sample for the current study ($N = 66$), descriptive analysis was performed for the categorical and ordinal sociodemographic variables. It was noted at this stage that both the ancestry and employment status variables required further coding, hereunder described.

Several participants had indicated on the online questionnaire that they were both “Employed” and “Student” but other participants had indicated that they were both

“Unemployed” and “Student” (as indicated below in Figure 5.2). This was therefore recoded so as to include student participants as employed. In addition, individuals indicating either “Home executive” or “Retired” were recoded into one group as unemployed participants. One individual indicated that they were both “Board retrenched” and “Home executive” and was therefore recoded into the unemployed group.

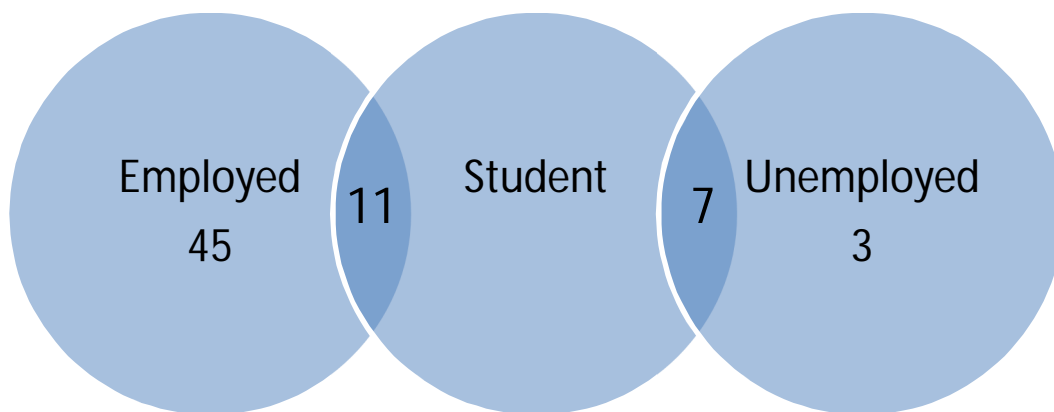


Figure 5.2. Venn diagram to indicate questionnaire answer overlap.

Participants were asked to select their ancestry from Africa, Asia, Central America, Europe, North America, Pacific Australia New Zealand, South America, and unknown ancestry. They were also able to select multiple ancestries on the questionnaire. Therefore, individuals were grouped based on their selections into mixed heritage (participants who selected two or more ancestries), African heritage, Asian heritage, European heritage, and unknown heritage (participants who indicated that they did not know their ancestry).

Following completion of frequency analysis, age was explored and then further assessed for normal distribution. Distribution was investigated using the Shapiro-Wilk test and calculations of skewness and kurtosis.

A comparison between the MO and control groups for all sociodemographic variables was then performed. With respect to the categorical and ordinal items, cross-tabulations and the χ^2 test were used. In groups where a large amount of cells had counts of less than five, the Fisher's Exact test was used rather than the unsuitable χ^2 test (Field, 2009). For the interval variable, age, the two groups were compared using the Mann-Whitney U-test.

The temperament dimensions and subdimensions were then explored and their distributions assessed for normality using the Shapiro-Wilk test and calculations of skewness and kurtosis. Results from the TPQ were scored by the Anthropedia Foundation in accordance with their policy regulating the use of the questionnaire. The Anthropedia Foundation then supplied the researcher with the reliability and factor structure of the TPQ for the sample. The data for NS, NS4, HA, and RD was normally distributed and therefore parametric tests were used. However, the results from the P dimension and all other subdimensions indicated non-normally distributed curves. Tests using these variables therefore required non-parametric tests.

With regards to ELISA data, the average absorbance values (OD) for each set of the duplicate standards and the duplicate samples were calculated (Abcam, n.d., 2015a). This was first done manually by the researcher for four samples in the following manner: The average net OD was calculated by subtracting the average NSB OD from the average OD bound (Abcam, 2015a); Average net OD = Average bound OD – Average NSB OD. Thereafter, the binding of each pair of the standard wells is calculated as a percentage of the maximum binding wells (Abcam, 2015a); Percent bound = (Net OD/ Net Bo OD) \times 100

The online software programme MyAssay (Cook, 2009) was used to plot the Percent bound (%) versus Serotonin concentration (pg/mL) for the standards. The R^2 values were higher than .95 and therefore a good fit was provided with a 4 parameter logistic algorithm. Manual calculations were used to ensure that the Percent bound values rendered were correct. The sample concentrations were then calculated using the appropriate standard curve by MyAssay as well as the CV (Abcam, 2015a; Cook, 2009). The descriptive statistics for the serum serotonin concentration were then calculated. The data was non-normally distributed and therefore non-parametric tests were used.

In order to check for confounding sociodemographic variables with the independent variable of temperament dimension score, the independent sample *t* test and the Spearman's rank order correlation test were performed. It was found that only age and unknown ancestry were significantly associated with P and this was therefore controlled for in later analyses.

The independent sample *t* test was used to assess the relationship between migraine and NS, HA, and RD. The Mann-Whitney U-test assessed the relationship between migraine and P as well as between migraine and serum serotonin concentration. The Spearman's rank order correlation test was run to ascertain associations between temperament and serum serotonin concentration. The latter test was also used to assess associations between the temperament dimensions and subdimensions.

5.3. Sociodemographic data

The sample consisted of 43 MO patients ($n = 43$; 65.2%) as well as 23 controls ($n = 23$; 34.8%). Sociodemographic variables for the two groups were compared between MO participants and healthy controls.

The central tendency data for age is shown in Table 5.1. The mean age for the MO group was 36.6 years ($SD = 11.2$), and 38.8 years for the control group ($SD = 11.5$). The p value indicated that there was no significant difference between the two groups.

Table 5.1.

Mean and SD of age for MO and controls

	MO			Control			p
	n (%)	M	SD	n (%)	M	SD	
Age* (y)	41 (95.3)	36.6	11.2	22 (95.7)	38.8	11.5	.48

*Three participants did not complete this item (two from the MO group and one from the control group)

The overall mean age was 37.4 years ($SD = 11.2$, age range = 20-63). The Shapiro-Wilk test ($W(63) = .92$, $p = .001$), $z_{skewness}$ value ($p < .10$), and $z_{kurtosis}$ value ($p < .10$) were significant indicating a positively skewed, platykurtic distribution (Field, 2009). This was confirmed visually in a histogram graph, depicted in Figure 5.3 below, as well as in a Q-Q plot, Figure 5.4. Statistical analysis for this variable therefore used non-parametric measures.

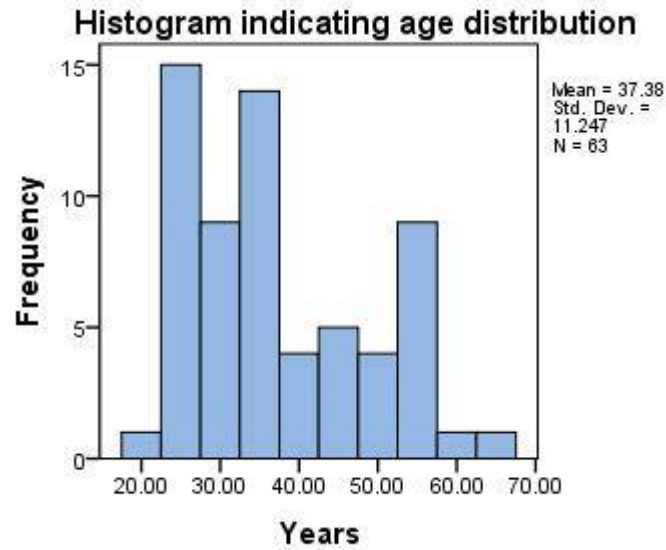


Figure 5.3: Histogram visually confirmed non-normal distribution of age (years).

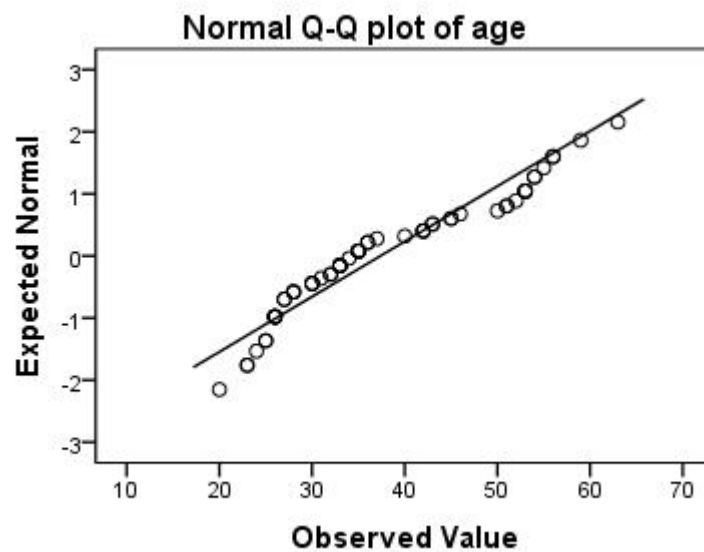


Figure 5.4: Q-Q plot visually confirmed non-normal distribution of age (years).

Table 5.2 shows the categorical and ordinal sociodemographic data. The majority of the participants had European ancestry, were female, and held a tertiary education qualification in both the migraine and control groups. The vast majority of participants for both MO and control groups were employed (97.7% and 91.3% respectively). Amongst migraine participants there was a history of psychiatric diagnosis in 36.4% of the group,

compared to 19% of the control participants. The p values indicated that there were no statistically significance differences between MO and control groups for gender, education level, employment status, language, ancestry, or history of psychiatric diagnosis.

Table 5.2.

Sex, education, ancestry, vernacular, employment status, and psychiatric history frequencies for MO and control

Variable	MO		Control		p (two-sided)
	n	%	n	%	
Male/female	4/39	9.3/90.3	5/18	21.7/78.3	.28
Education level:					1.00
High	2	4.7	1	4.3	
Tertiary	41	95.3	22	95.7	
Ancestry:					
Mixed ancestry	3	7.0	5	21.7	.12
African ancestry	4	9.3	1	4.3	.65
Asian ancestry	2	4.7	1	4.3	1.00
European ancestry	31	72.1	16	69.6	1.00
Unknown ancestry	3	7.0	0	0	.55
Language:					.82
First language English	25	58.1	11	47.8	
Employed	42	97.7	21	91.3	.28
History of psychiatric diagnosis	16*	37.2	6	26.1	.42

*One participant did not complete this item

5.4. Temperament dimensions

The means, standard deviations, and distributions for each of the four temperament dimensions for all participants who completed blood donation as well ($N = 66$) are indicated in Table 5.3 below. The NS temperament had a mean score of 14.7 ($SD = 6.18$) and a median of 15.0. The mean score for HA was 15.8 ($SD = 7.39$) with a median of 15.5. RD ($M = 12.1$,

$SD = 4.03$) had a median of 12.0. The final temperament, P, had a mean score of 5.92 ($SD = 1.85$) and a median of 6.0.

Table 5.3.

Temperament dimensions: Central tendency and assessment of normality

Temperament dimension	<i>M (SD)</i>	Skewness (SE)	Kurtosis (SE)	Shapiro-Wilk test
NS	14.7 (6.18)	-.17 (.30)	-.83 (.58)	W(66) = .97
HA	15.8 (7.39)	.08 (.30)	-.84 (.58)	W(66) = .98
RD	12.1 (4.03)	-.16 (.30)	-.78 (.58)	W(66) = .97
P	5.92 (1.85)	-.19 (.30)	-.69 (.58)	W(66) = .95*

* Significant at the $p < .05$ level

As indicated in Table 5.3 above, normality assessments were non-significant for the NS, HA, and RD temperament dimensions which were corroborated by their histogram and Q-Q plot graphs (Figures 5.5 to 5.10). Statistical analysis for these variables therefore relied on parametric measures. However, the Shapiro-Wilk test indicated a significant result for the P dimension ($W(66) = .95, p < .05$). Although $z_{skewness}$ and $z_{kurtosis}$ values were non-significant, visual examination of the histogram and Q-Q plots, Figures 5.11 to 5.12 below, indicated slight platykurtosis (Field, 2009). Based on the Shapiro-Wilk test and visual examination, the statistical analysis for this variable therefore used non-parametric measures.

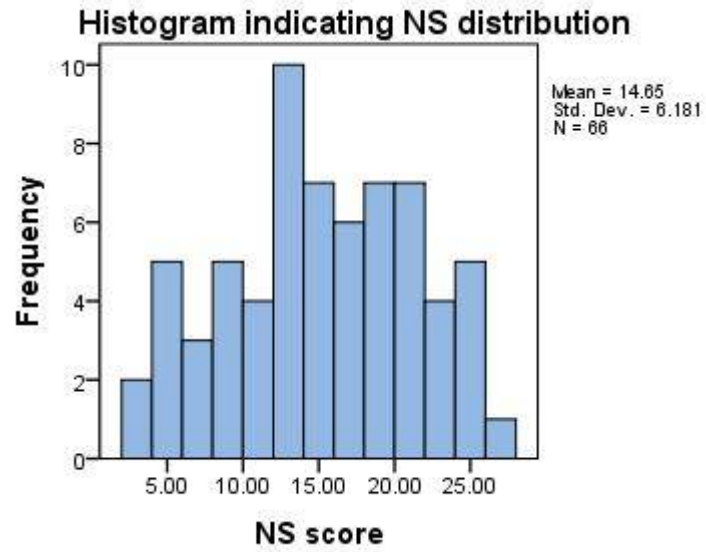


Figure 5.5: Histogram visually confirmed normal distribution of NS.

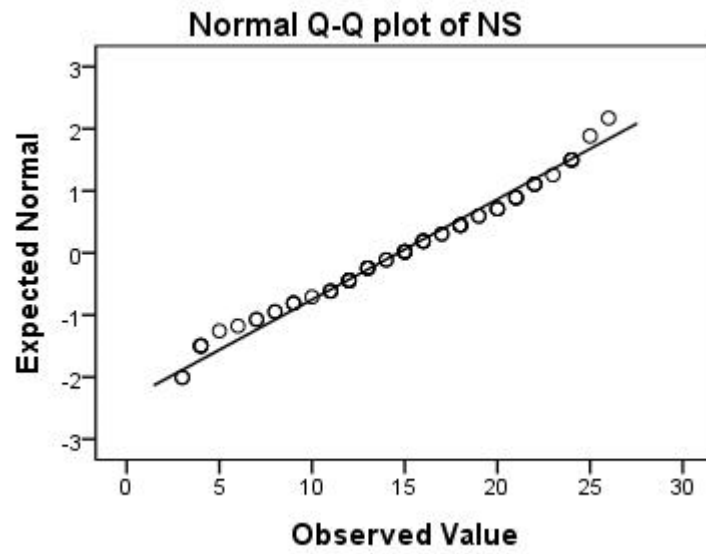


Figure 5.6: Q-Q plot visually confirmed normal distribution of NS.

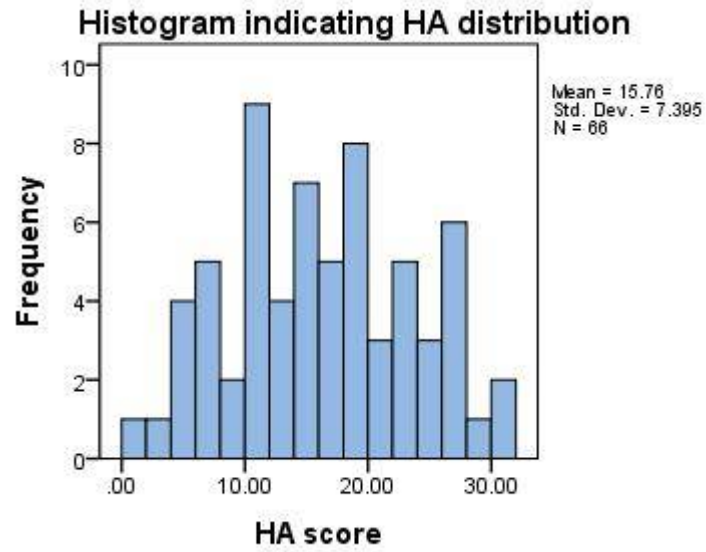


Figure 5.7: Histogram visually confirmed normal distribution of HA.

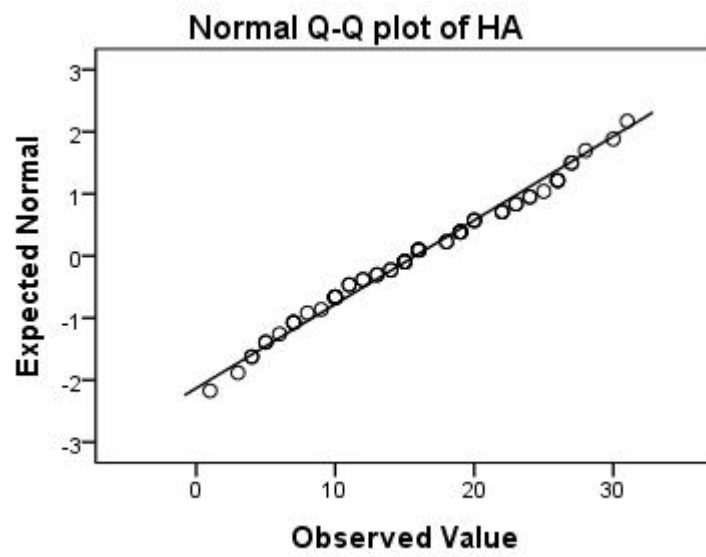


Figure 5.8: Q-Q plot visually confirmed normal distribution of HA.

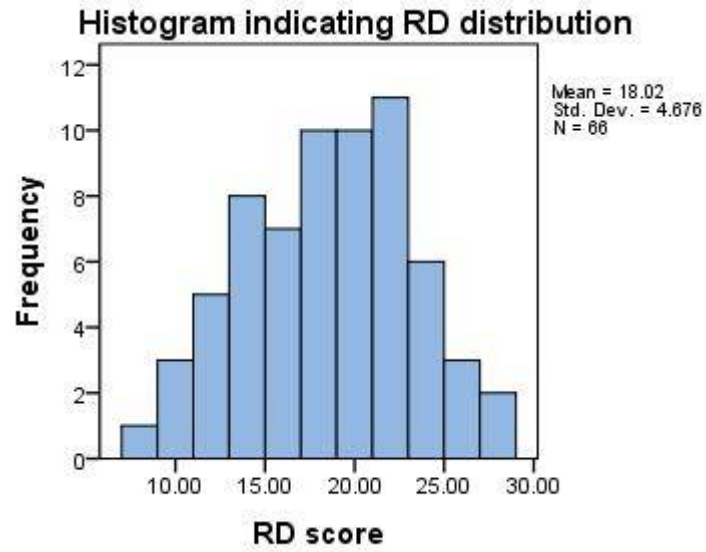


Figure 5.9: Histogram visually confirmed normal distribution of RD.

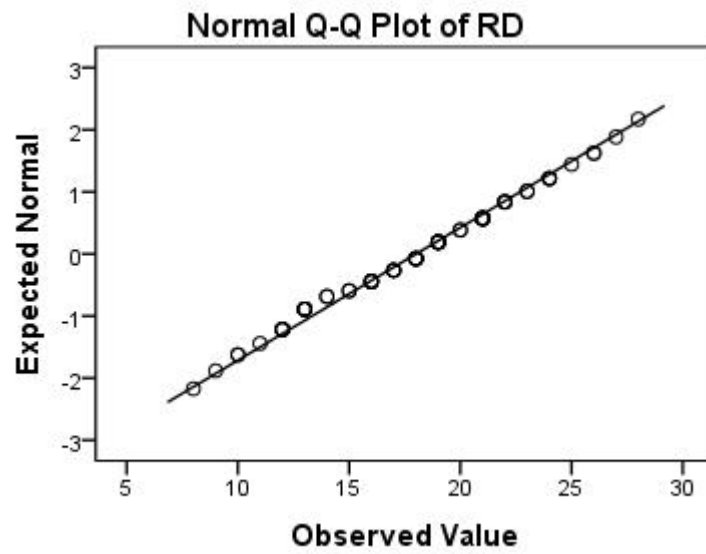


Figure 5.10: Q-Q plot visually confirmed normal distribution of RD.

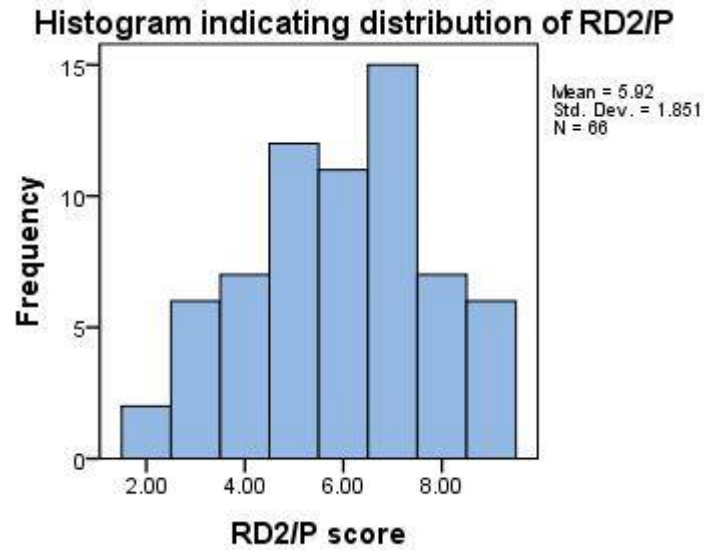


Figure 5.11: Histogram visually confirmed non-normal distribution of RD2/P.

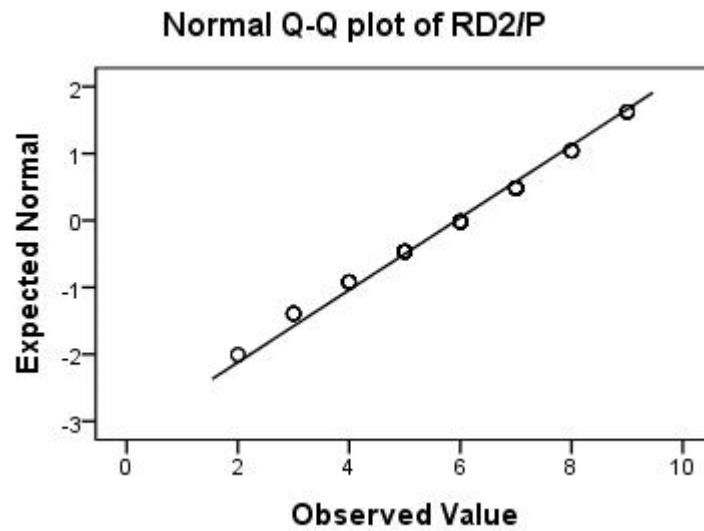


Figure 5.12: Q-Q plot visually confirmed non-normal distribution of RD2/P.

The individual TPQ subdimensions were explored separately using the same analysis steps as above (Table 5.4). The majority of the subdimensions evinced a non-normal distributed as indicated by the significant scores for the Shapiro-Wilk test. Analysis using the separate subdimensions therefore relied on non-parametric measures.

Table 5.4.

Temperament subdimensions: Central tendency and assessment of normality

Subdimension	<i>M</i> (<i>SD</i>)	Skewness (<i>SE</i>)	Kurtosis (<i>SE</i>)	Shapiro-Wilk test
NS1	4.68 (2.18)	-.25 (.30)	-.66 (.58)	W(66) = .96*
NS2	2.58 (2.17)	.51 (.30)	-.85 (.58)	W(66) = .91***
NS3	3.29 (2.13)	.02 (.30)	-1.0 (.58)	W(66) = .94**
NS4	4.11 (2.13)	-.12 (.30)	-.65 (.58)	W(66) = .96
HA1	4.18 (2.64)	.29 (.30)	-.83 (.58)	W(66) = .96*
HA2	4.15 (2.11)	-.27 (.30)	-.87 (.58)	W(66) = .93***
HA3	3.44 (2.24)	.02 (.30)	-1.2 (.58)	W(66) = .93***
HA4	3.98 (2.62)	.10 (.30)	-1.1 (.58)	W(66) = .94**
RD1	3.80 (1.19)	-1.01 (.30)	.66 (.58)	W(66) = .85***
RD3	5.47 (2.71)	.03 (.30)	-1.04 (.58)	W(66) = .95**
RD4	2.82 (1.39)	-.12 (.30)	-.86 (.58)	W(66) = .93***

* Significant at the $p < .05$ level; ** Significant at the $p < .01$ level; *** Significant at the $p \leq .001$ level

Scores from the TPQ were calculated by the Anthropedia Foundation. In the larger study, a total of 324 participants completed the online questionnaires which included the TPQ ($N = 324$, $M_{\text{age}} = 36.7$, $SD = 11.7$, age range = 18-72). This data was provided to the foundation who then supplied the reliability and factor structure of the TPQ. To assess internal consistency of the TPQ the Cronbach α was used and is reported in Table 5.5 below. The internal consistency coefficients for the three temperaments NS ($\alpha = .78$), HA ($\alpha = .90$), and RD ($\alpha = .72$) were considered good, excellent, and acceptable, respectively. The Cronbach α for the fourth temperament dimension P/RD2 ($\alpha = .56$) is considered poor. However, it should be noted that the value of α is influenced by the number of items in the scale, i.e. α increases as the number of items increases (Field, 2009). As P was originally conceptualised as part of RD, it has fewer items than the other scales.

Table 5.5.

TPQ: Scale and subdimension number of items and Cronbach alphas

Subdimension	Number of items	Cronbach's α
NS1	9	.55

Subdimension	Number of items	Cronbach's α
NS2	8	.67
NS3	7	.69
NS4	10	.53
NS	34	.78
HA1	10	.80
HA2	7	.76
HA3	7	.79
HA4	10	.81
HA	34	.90
RD1	5	.38
RD3	11	.75
RD4	5	.53
RD	21	.72
P	9	.56

*The Anthropedia Foundation used the data from all participants who completed the online questionnaire ($N = 324$)

The factor structure of the TPQ was also provided by the Anthropedia Foundation and is indicated in Table 5.6. A principal component analysis was performed and rotated using Varimax with Kaiser Normalization. Overall, a three-factor model based on the underlying temperament dimensions proposed provided a good approximation of the data. Respectively, components one, two, and three represent the HA, NS, and RD scales. Two subdimensions were apparently misplaced as they did not load on their hypothesized scales.

The NS1 subdimension, “Exploratory excitability versus stoic rigidity”, loaded negatively on the first (HA scale) rather than second dimension (NS scale). However, this result is not fully inconsistent as HA is considered to regulate NS in a limited capacity (Bagby et al., 1992). An additional exception was the RD2 subdimension which loaded negatively on the second component (NS scale) rather than the RD scale. However, this was to be expected as it has been noted that the RD2 subdimension represents a fourth temperament dimension, P, rather than RD.

Table 5.6.

TPQ: Factor structure

Subdimension	Component		
	<u>1</u>	<u>2</u>	<u>3</u>
NS1	-.513	.366	
NS2		.652	
NS3		.730	
NS4		.713	
HA1	.813		
HA2	.780		
HA3	.758		
HA4	.679		
RD1			.695
RD3			.679
RD4	.328		.677
RD2/P		-.488	.387

Extraction method: Principal Component Analysis.

Rotation method: Varimax with Kaiser Normalisation. a. Rotation converged in five iterations.

5.5. Serum serotonin concentration

Means, standard deviations, distributions and frequencies for the serum serotonin concentration variables were calculated and are given in Table 5.7. For the sample ($N = 66$), the mean score was 409 pg/mL ($SD = 399$, range = 29.6 – 1949).

Table 5.7.

Serotonin concentration means and standard deviations

	<i>MO</i>		<i>Control</i>	
	<u><i>M</i></u>	<u><i>SD</i></u>	<u><i>M</i></u>	<u><i>SD</i></u>
Serum [serotonin]	392	421	440	363

The Shapiro-Wilk test was highly significant ($p = .000$) as were $z_{skewness}$ and $z_{kurtosis}$ values ($p < .0001$) indicating a non-normal distribution. In addition the histogram and Q-Q

plot graphs for this variable indicated positive skewness and a leptokurtic curve (Figures 5.13 and 5.14) (Field, 2009).

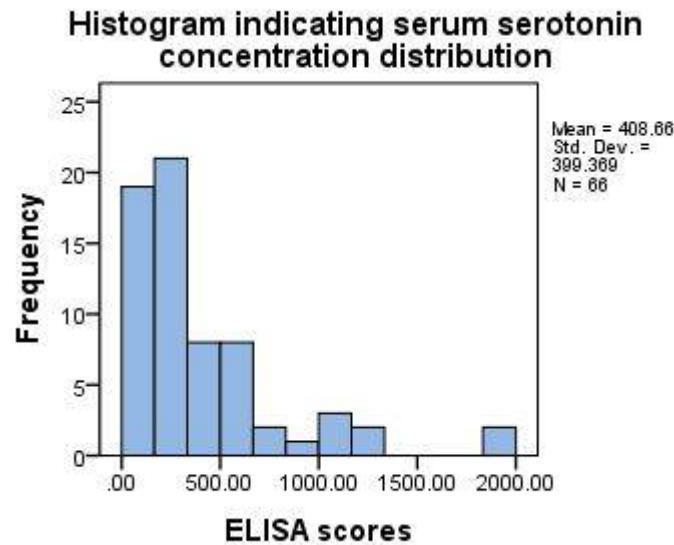


Figure 5.13: Histogram visually confirmed non-normal distribution of serotonin concentration scores

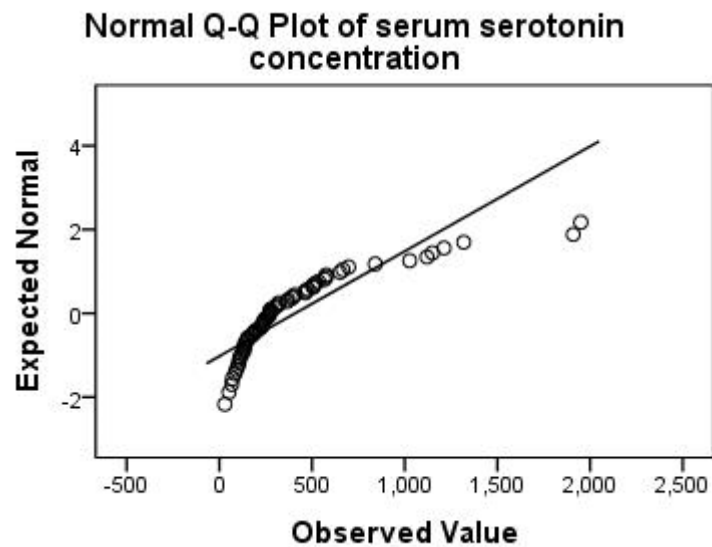


Figure 5.14: Q-Q plot visually confirmed non-normal distribution of serotonin concentration scores

The online computer software used to determine the serum serotonin concentration also rendered the CV values (Cook, 2009). These were averaged for each plate which

rendered percentages of 21.7, 16.7, and 14.7, respectively. These values are higher than the 11.0% given in the Abcam protocol booklet for low serotonin concentrations indicating that precision was low for all three assays (Abcam, 2015b).

5.6. Confounding variables

Preliminary correlation analyses were performed in order to ascertain whether the demographic variables gender, age, ethnicity, and ancestry were confounded with the independent variables, the temperament dimensions. In the design of the study, matching of age and gender was used as far as possible to select a control group to limit these potential effects. However, further techniques, such as randomization, were not possible and therefore statistical methods are necessary (Pourhoseingholi, Baghestani, & Vahedi, 2012). Factors which have been implicated in previous studies included gender, age, and education level. These factors are therefore discussed in further detail below although it is noted here that ancestry, language, employment status, and history of psychiatric diagnosis were assessed. Spearman's rank order correlation coefficient was used which did not indicate significant correlations, other than for a significant association between P and unknown ancestry, ($r_s[62] = -.32, p = .01$). Therefore, this was controlled in later analyses.

5.6.1. Gender

With regards to gender, it has generally been found that females score higher than males on both the HA dimension (Cloninger et al., 1991; Miettunen et al., 2006; Nixon & Parsons, 1989; Otter et al., 1995; Stewart et al., 2004; Waller et al., 1991) and on the RD scale (Cloninger et al., 1991; Nixon & Parsons, 1989; Otter et al., 1995; Stewart et al., 2004).

Furthermore, when Cloninger et al. (1991) assessed the psychometric properties of the TPQ in a sample consisting of 326 white men ($M_{age} = 43.6, SD = 16.4$), 350 white women ($M_{age} = 45.3, SD = 17.8$), 136 black men ($M_{age} = 43.6, SD = 18.1$), and 217 black women ($M_{age} = 43.2, SD = 18.1$) ($N = 1029$), the data indicated that men scored higher than women on NS. However, the study performed by Nyman et al. (2009) reported that female participants scored higher than males on all temperament dimensions except PS.

Although normally distributed, a nonparametric procedure, the Spearman's rank order correlation coefficient (i.e. Spearman's rho) was conducted to compare the total score for the NS, HA, and RD temperament dimensions for males and females due to small group sizes and the large differences between the number of men and women. There were no significant differences for any of the four temperament dimensions between male and female participants indicating that gender was not a confounding variable. As indicated previously, P was non-normally distributed. Accordingly, the Spearman's rho was again performed. No significant difference was identified across gender.

5.6.2. Age

A negative relationship between NS and age has been reported (Cloninger et al., 1991; Otter et al., 1995). Following additional regression analysis of NS on age by Cloninger et al. (1991), the data indicated that NS scores decline by approximately one point per decade.

Age was positively skewed and therefore the Spearman's rho was performed. The Spearman's rho revealed a statistically significant relationship between age and P ($r_s[62] = -.27, p < .05$). This was controlled for in later analyses.

5.6.3. Education level

Cloninger et al. (1991) reported that white participant scores on the NS dimension had a positive correlation with years of education for both genders ($r_{male} = .12, p < .05$; $r_{female} = .19, p < .001$). It has been reported that HA increases with education level (Miettunen et al., 2004). However, Cloninger et al. (1991) noted that there were no correlations between HA and years of education other than a negative association among both white and black female participants ($r_{white} = -.24, p < .001$; $r_{black} = -.21, p < .01$), which is additionally contradictory in sign to the association reported by Miettunen et al. (2004). RD further did not show a significant association with years of education other than a significant correlation amongst white female scores ($r = .21, p < .001$).

Spearman's rho was used to assess the possible relationship between education level and temperament scores for the main dimensions. No significant associations were indicated.

5.7. Comparison between MO and control groups

The MO and control groups were compared across a number of variables. Each comparison is discussed separately under the following headings.

5.7.1. Temperament dimension scores

The mean scores for each temperament and its subdimensions as measured by the TPQ are indicated in Table 5.8 for both the MO and the control group. The TPQ NS, HA, and RD dimensions indicated normality; consequently, the Student's t test was used to investigate the first hypothesis (association of migraine with HA) for these dimensions. All tests were performed with an alpha of 0.05, two-tailed (de Melo Santos et al., 2011).

Table 5.8.

Mean scores on TPQ dimensions for MO and control groups

Dimensions and subdimensions	<i>MO</i>		<i>Control</i>	
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>
NS1 Exploratory excitability vs stoic rigidity	4.77	2.07	4.52	2.41
NS2 Impulsiveness vs reflection	2.79	2.16	2.17	2.19
NS3 Extravagance vs reserve	3.53	2.13	2.83	2.10
NS4 Disorderliness vs regimentation	4.35	2.18	3.65	2.01
NS Novelty seeking	15.44	5.97	13.17	6.44
HA1 Worry and pessimism vs optimism	4.81	2.50	3.00	2.54
HA2 Fear of uncertainty vs confidence	4.53	2.11	3.43	1.95
HA3 Shyness with strangers vs gregariousness	3.58	2.14	3.17	2.44
HA4 Fatigability and asthenia vs vigor	4.58	2.43	2.87	2.65
HA Harm avoidance	17.51	7.01	12.48	7.10
RD1 Sentimentality vs insensitiveness	3.86	1.13	3.70	1.33
RD3 Attachment vs detachment	5.60	2.80	5.22	2.59
RD4 Dependence vs independence	2.84	1.53	2.78	1.13
RD Reward dependence	12.30	4.15	11.70	3.87
RD2/P Persistence vs irresoluteness	5.79	1.92	6.17	1.72

However, P and the majority of the subdimensions indicated a non-normal distribution and therefore the Mann-Whitney test was used for these calculations. The results of these analyses are indicated in Table 5.9. MO participants scored significantly higher than the control group on the HA1, HA2, and HA4 subdimensions as well as the HA scale itself. All other subdimensions and scales were non-significant.

Table 5.9.

Comparison of TPQ dimensions between the migraine and control groups

Dimensions and subdimensions	<i>t</i> (64)	<i>p</i> (two-tailed)
NS4	-1.27	.21
NS	-1.43	.16
HA	-2.77	.01**
Dimensions and subdimensions	<i>t</i> (64)	<i>p</i> (two-tailed)
RD	-.58	.56
Dimensions and subdimensions	<i>U</i> (64)	<i>p</i> (two-tailed)
NS1	475	.79
NS2	408	.24
NS3	402	.21
HA1	290	.01**
HA2	328	.02*
HA3	442	.48
HA4	309	.01*
RD1	468	.71
RD3	452	.57
RD4	477	.80
RD2/P	435	.42

* Significant at the $p < .05$ level; ** Significant at the $p \leq .01$ level

5.7.2. Serum serotonin concentration

The Mann-Whitney U test was used to investigate the association between migraine and serotonin concentration. The results ($U(64) = 434$, $p = .42$) indicated that there was no significant difference between the MO and control groups, the third hypothesis.

5.8. Temperament scores and serum serotonin concentration

Spearman's correlation tests were used to investigate correlation between TPQ dimensions and serotonin scores, the third hypothesis. No significant correlations were

indicated between any of the main dimensions or their subdimensions and serum serotonin concentration. These results are indicated in Table 5.10. Following this a partial correlation was run controlling for both age and unknown ancestry, as it was indicated previously that these variables were significantly associated with P, but again there were no significant correlations identified.

Table 5.10.

Associations between temperament dimensions and subdimensions and serotonin concentration scores

Dimensions and subdimensions	rs[64], <i>p</i> (two-tailed)
NS1	.02
NS2	-.01
NS3	-.02
NS4	.01
NS	.00
HA1	-.14
HA2	.04
HA3	-.02
HA4	-.16
HA	-.11
RD1	-.11
RD3	-.08
RD4	.04
RD	-.08
RD2/P	.00

5.9. Temperament dimension and subdimension correlations

Partial Spearman’s rho was used to assess whether there were significant associations between the temperament dimensions and subdimensions. This was performed in order to assess how the TPQ performed in this study.

Partial correlations (controlling for age and unknown ancestry) were automatically run with Pearson correlations by SPSS but needed to be recoded. NS was negatively

correlated with both HA and P, but positively correlated with RD. Correlations between HA and RD were both positive (HA4 α RD1, $r_{s[59]} = .29, p < .05$; HA4 α RD4, $r_{s[59]} = .28, p < .05$; HA α RD4, $r_{s[59]} = .26, p < .05$) and negative (HA3 α RD3, $r_{s[59]} = -.30, p < .05$). RD1 was significantly correlated with P ($r_{s[59]} = .28, p < .05$).

When compared across groups, the control group was too small for the analysis. In the MO group, significant negative correlations were noted between NS and HA, significant correlations were found between NS and RD, and both positive and negative correlations were identified between HA and RD. In the latter, the positive correlation was between HA4 and RD1 ($r_{s[37]} = .34, p < .05$) and the negative correlation was between HA3 and RD3 ($r_{s[37]} = -.32, p = .05$). The significant associations are presented in Table 5.11 on the following page.

5.10. Summary of chapter

Prior to comparing the two groups with regards to temperament dimensions, it was confirmed whether any of the sociodemographic variables acted as confounding variables. Only age and unknown ancestry were significantly associated with P and this was therefore controlled for during later analyses. The results indicated that the MO and control groups did not differ significantly on sociodemographic variables. When comparing the temperament dimensions and subdimensions between groups, it was indicated that the MO participants scored significantly higher on the HA1, HA2, and HA4 subdimensions as well as the HA scale itself. There were no significant differences between serotonin concentration for the two groups and this variable was also not significantly related to any of the temperament dimensions or subdimensions. There were several significant correlations between the

temperament dimensions and subdimensions for the sample ($N = 66$) as well as for the MO group. In the next chapter, these findings are further explored and final conclusions are drawn. Recommendations are made and then the strengths and limitations of the study are presented before the chapter concludes.

Table 5.11.

Associations between temperament dimensions and subdimensions

Both MO and control groups; rs[59], <i>p</i> (two-tailed)								
	HA2	HA3	HA	RD1	RD3	RD4	RD	P
NS1	-.42 (.00)***	-.29 (.02)*	-.35 (.01)**					
NS2						.30 (.03)*	.29 (.03)*	
NS3							.27 (.04)*	-.28 (.03)*
NS4					.28 (.03)*		.29 (.03)*	
NS	-.26 (.04)*				.26 (.04)*			
HA3					-.30 (.02)*			
HA4				.29 (.03)*		.28 (.03)*		
HA						.26 (.05)*		
RD1								.28 (.03)*
MO group only; rs[59], <i>p</i> (two-tailed)								
	HA2	HA3	HA	RD1	RD3	RD4	RD	P
NS1	-.34 (.03)*		-.38 (.02)*					
NS2	-.38 (.02)*							
NS3								
NS4		-.32 (.05)*						
NS	-.34 (.04)*					.32 (.04)*	.33 (.04)*	
HA3					-.32 (.05)*			
HA4				.34 (.04)*				
HA								
RD1								

* Significant at the $p \leq .05$ level; ** Significant at the $p \leq .01$ level; *** Significant at the $p \leq .001$ level

CHAPTER 6: DISCUSSION

This chapter firstly provides a brief overview of the study, including the aims and rationale. Thereafter follows an interpretation and discussion of the results in relation to the three research questions of the study, Cloninger's Psychobiological Theory of Personality, and the proposed migraine model, for which varying degrees of support were identified. Following discussion of the results, recommendations are made for further research as well as, where appropriate, real-life application. In addition, both the limitations and contributions of the study are discussed before presenting a final conclusion.

6.1. Overview of the study

Migraine is a common pain disorder with a high prevalence in South Africa (Health24, 2014; Leaders in Wellness: The Business of Health, 2014; Migraine Research Institute, n.d.-b). However, a clear and defined cause is yet to be determined (Cahill et al., 2014; Gasparini et al., 2013; Schürks et al., 2011). Beyond its physical effects and chronic pain, migraine also impacts emotional and social functioning (Bakar et al., 2015). This indicates that there are both physiological and psychological aspects involved in migraine disorder processes. Studies of the former have provided evidence of neurotransmitter imbalances, whilst the latter has reference to personality (Katon et al., 2011; Schürks et al., 2011). Attempts to provide a more holistic view of migraine, which take into account the interaction between biology and psychology, may provide valuable insight. This study therefore sought to explore the relationship between temperament and the serotonin neurotransmitter in MO patients.

Cloninger's Psychobiological Theory of Personality includes four temperament dimensions and three character traits (Mochcovitch et al., 2012; Verweij et al., 2010; Zuckerman, 1995). A 'migraine personality' has been proposed which presents as a particular personality profile characterised by both anxious and depressive traits. The HA temperament dimension is purported to be a defining characteristic of this personality. The HA temperament is theoretically underpinned by serotonin in Cloninger's theory (Abbate-Daga et al., 2007; Montag, 2014). The first aim of this study was therefore to explore if there was a covariance between mean temperament scores and serum serotonin concentration in MO patients and controls, while the second aim of this study was to investigate whether the MO group displayed a temperament score distribution featuring a higher HA score in comparison to the control group. In addition, serotonin has also been implicated in migraine. Therefore, a migraine model was proposed in this study which linked migraine and HA with a common underpinning serotonergic system. Thus, three associations were proposed in the model and explored in this research: MO and HA; HA and serotonin; and MO and serotonin.

In order to accomplish these aims, MO patients ($N = 43$) and controls ($N = 23$) were assessed using the TPQ to assess temperament and ELISAs to measure serum serotonin concentration. This study was a non-experimental quantitative correlation study using a post-positivist paradigm. With regards to the first aim, the data were analysed using Spearman's Rho correlation coefficients whilst, for the second aim, either the independent samples t test or the Mann-Whitney U-test checked for relationships between migraine and the temperament score distribution as well as with serum serotonin concentration.

6.2. Migraine and temperament

There are four temperament dimensions identified in Cloninger's Psychobiological Theory of Personality: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD), and Persistence (P). The temperament traits are expected to have a genetic basis, are exhibited early in life, and form automatic responses to emotional stimuli (Ando et al., 2004; Celikel et al., 2009; Cloninger et al., 1998, 1993; Cloninger, 1999).

Analyses indicated that the MO participants scored significantly higher than their control group counterparts on the HA dimension [$t(64) = -2.77, p = .01$] and on several of its subdimensions, i.e. HA1 [$U(64) = 290, p = .01$], HA2 [$U(64) = 328, p < .05$], and HA4 [$U(64) = 309, p = .01$]. All other dimensions and subdimension were non-significant. Therefore, the null hypothesis is rejected and the alternative is accepted: A high mean HA score is associated with MO.

This result therefore lends credence to the proposal of a personality profile specific to migraine sufferers. The 'migraine personality' reported by Wolf in 1937, and supported in the literature, is characterised by both anxious and depressive traits (Gentili et al., 2005; Merikangas, Merikangas, et al., 1993; Merikangas, Stevens, et al., 1993; Pompili et al., 2010). The temperament dimension HA is seen as a heritable bias towards inhibiting behaviours in response to cues of punishment or non-reward (Knaster et al., 2012; Miettunen et al., 2006, 2007; Peirson et al., 1999). These behaviours include pessimistic worry regarding anticipated problems, passive avoidance behaviours such as shyness, and high fatigability (Cloninger et al., 1993; Elovainio et al., 2004). High HA individuals are typically

wary, tense, hesitant, and pessimistic (Nelson & Cloninger, 1995, 1997) whilst those who score low on this temperament tend towards low anxiety or fear (Cloninger et al., 1997).

A high score on HA is also consistent with the avoidance behaviour often developed by chronic pain sufferers to situations they associate with harm (Di Piero et al., 2001; Mongini et al., 2005; Sánchez-Román et al., 2007). Cloninger acknowledged that repeated exposure to aversive events could increase HA behaviours and sensitisation to perceived or expected harm whilst decreasing both NS and RD behaviours (Cloninger, 1987). Therefore, a high HA score may reflect a tendency to anticipate pain with pessimistic, negative, and fearful thoughts (Gustin et al., 2016). The subsequent cycle in which pain perception worsens the pain experience is described in the fear-avoidance model (Bussone et al., 2012; Bussone & Grazi, 2013). Identification of migraine sufferers with this ‘migraine personality’ can further assist in the treatment of migraine patients by including treatment aimed at emotions and cognitions regarding pain.

The finding of high HA amongst migraine sufferers in the current study is similar to that of previous studies (Di Piero et al., 2001; Mongini et al., 2005; Park et al., 2006; Sánchez-Román et al., 2007; Villani et al., 2010). Although the study by Nylander et al. (1996) indicated a lack of significant association between HA and migraine, it could be that Nylander’s results do not generalise to the South African context due to strict inclusion criteria used for participant selection (i.e. all participants were from one Swedish family in order to control for genetic heterogeneity).

The current study also assessed the relationships between migraine and each of the HA subdimensions. HA1 (worry and pessimism vs optimism), HA2 (fear of uncertainty vs

confidence), and HA4 (fatigability and asthenia vs vigour) were all significantly higher in the MO group. This is consistent with both the proposed personality profile as well as the impact of migraine on a patient's quality of life. Sánchez-Román et al. (2007) described similar findings; however, their study also revealed a significantly higher result for HA3 (shyness with strangers vs gregariousness). This difference could be as a result of participant heterogeneity between the two studies, small sample size of the current study, a unique identifier of the South African migraine population, or the wider influence of the South African context including perception of migraine.

In keeping with the findings presented by Villani et al. (2010), the results did not indicate any significant differences between the two groups for any of the other temperament dimensions or their subdimensions. However, this contradicts the finding of a lower NS score (Di Piero et al., 2001; Villani et al., 2010) and a higher score on the P temperament (Mongini et al., 2005) for migraine sufferers compared to controls. In fact, although not significant, the MO participants indicated higher NS and RD scores as well as lower P scores. This is unexpected as a high HA, a feature indicated by the MO participants, theoretically exerts a modulatory effect on NS and RD to inhibit these tendencies as a coping mechanism (Cloninger, 1987). This theoretical modulation is discussed in further detail below when the results of the intercorrelations between temperament dimensions and subdimensions are presented.

This result therefore lends credence to the hypothesis of a 'migraine personality' and also supports HA as a distinguishing characteristic of this personality. In so doing, the construct validity of HA as well as the migraine model proposed in this study are thus far supported.

6.2.1 The properties of the TPQ

In order to more fully explore Cloninger's theory and the relationship between MO and temperament, as well as evaluate the performance of the TPQ in this study, associations between the temperament dimensions were assessed both for the whole sample as well as for only the MO participants. Results indicated that for both groups there were associations between NS and HA, HA and RD, NS and RD, and NS and P. There were significant associations between NS1 and HA2 ($r_{s[59]} = -.42, p = .00$), HA3 ($r_{s[59]} = -.29, p = .02$), and HA ($r_{s[59]} = -.35, p = .01$) as well as between NA and HA2 ($r_{s[59]} = -.26, p = .04$).

Briefly, NS refers to the heritable tendency to activate behaviours aimed at exploration, excitement when confronted with novelty, approach to cues of reward, and active avoidance of monotony or frustration (Cloninger et al., 1993; Elovainio et al., 2004; Miettunen et al., 2006, 2007; Nelson & Cloninger, 1995, 1997). Individuals who score highly on this dimension are usually impulsive decision makers and short-tempered (Cloninger et al., 1993, 1997; Elovainio et al., 2004; Nelson & Cloninger, 1995, 1997). Low NS scores are indicative of individuals who are reflective and follow rules and regulations (Cloninger et al., 1997). This temperament dimension is proposed to reflect dopaminergic activity (Elovainio et al., 2004; Nelson & Cloninger, 1995, 1997). Given the typical presentation of an individual high in this temperament dimension, it is therefore unsurprising that there were negative associations with the HA dimension. However, what is noteworthy is that the NS dimension itself did not show a significant association with the HA dimension.

This lack of correlation between NS and HA deviates from evidence found by Giancola et al. (1994) and Nixon and Parsons (1989) as well as what would have been

expected based on Cloninger's theory (Cloninger, 1987). As stated before, it was suggested by Cloninger (1987) that the HA temperament modulates the activity of the NS and RD dimensions in order to balance between impulsively seeking new experiences and excessively persisting without reward. Cloninger predicted that there would therefore be a negative association between NS and HA (Cloninger, 1987; Giancola et al., 1994; Nixon & Parsons, 1989). Therefore, there should be a negative correlation between NS and HA in this sample as, despite the small size, these two dimensions were normally distributed.

The modulation referred to above also led Cloninger (1987) to predict a weak positive relationship between HA and RD (Cloninger, 1987; Giancola et al., 1994; Nixon & Parsons, 1989). RD is a heritable tendency to respond strongly to reward signals with continuation of the behaviour, especially to those indicating social approval (Cloninger et al., 1993; Elovainio et al., 2004; Miettunen et al., 2006, 2007). High RD individuals are likely to be warm, sentimental, form social attachments easily, dependent, and sociable (Cloninger et al., 1993; Nelson & Cloninger, 1995, 1997). Those who score low on this dimension may tend towards aloofness and insensitivity to social signals (Cloninger et al., 1997). Noradrenergic activity is associated with this temperament dimension (Elovainio et al., 2004; Nelson & Cloninger, 1995, 1997).

In the current study, RD1 was significantly correlated with HA4 ($r_{s[59]} = .29, p = .03$), RD3 was correlated with HA3 ($r_{s[59]} = -.30, p = .02$), and RD4 was significantly associated with HA ($r_{s[59]} = .26, p = .05$) and HA4 ($r_{s[59]} = .28, p = .03$). It is logical that RD1 (sentimentality vs insensitiveness) would be positively related to HA4 (fatigue and asthenia vs vigour) as an individual more likely to be energetic and vigorous may at times also tend to be more critical or insensitive. RD4 (dependence vs independence) would also be

expected to be related to HA as their tendency to be fearful, shy, or easily fatigued may be linked to a higher level of dependence. The RD3 subdimension (attachment vs detachment) was significantly negatively associated with HA3 (shyness with strangers vs gregariousness). This association may be that individuals who are shy may be more detached in their interpersonal interactions. Thus, there are some positive associations but not only do these results disagree with the expected correlation between HA and RD dimensions, rather than only subdimensions, but there was also a negative correlation where positive associations are expected.

It can also be noted at this juncture that Cloninger (1987) proposed that a child high in both HA and RD is likely to develop chronic anxiety if in an aversive situation where safety cannot be reliably determined. In addition, a child with this temperament profile may develop reactive depression due to frustration if there is a loss of control over rewards (Cloninger, 1987). The current study did not assess anxiety or depression and therefore cannot draw inferences regarding its relationship with migraine. However, the sample did indicate a relatively high percentage of MO participants who had been previously diagnosed with a psychiatric disorder (38.1%) and migraine, which has been associated with both anxiety and depression, can be considered an aversive situation.

Cloninger did not anticipate any significant relationship between NS and RD (Cloninger, 1987; Giancola et al., 1994; Nixon & Parsons, 1989). However, the study at hand identified associations between RD3 and NS4 ($r_{s[59]} = .28, p = .03$), RD3 and NS ($r_{s[59]} = .26, p = .04$), RD4 and NS2 ($r_{s[59]} = .30, p = .03$), RD and NS2 ($r_{s[59]} = .29, p = .03$), RD and NS3 ($r_{s[59]} = .27, p = .04$), as well as RD and NS4 ($r_{s[59]} = .29, p = .03$). Given that there was not an expected relationship, the lack of significant association between the main

dimensions of NS and RD is understandable. What is less so are the various correlations involving the subdimensions. However, when considering that RD correlated with impulsiveness (NS2), extravagance (NS3), and disorderliness (NS4), it could be that in the pursuit of reward the individual may behave in a manner typical of high NS if the behaviour results in positive feedback. Therefore, there is logic to these associations in keeping with the interaction at the level of the temperament dimensions proposed by Cloninger, but confirmation of this association and further research is required.

P was included as a temperament dimension relatively late and therefore Cloninger (1987) did not make reference to its interconnections. P was significantly associated with NS3 ($r_{s[59]} = -.28, p = .03$) and with RD1 ($r_{s[59]} = .28, p = .03$). P is a heritable bias towards persevering in behaviour despite intermittent reward (Cloninger et al., 2012; Elovainio et al., 2004; Miettunen et al., 2006, 2007). Individuals who rank high on this dimension are typically described as hard-working, steady, and diligent (Nelson & Cloninger, 1995, 1997) whereas those with low scores on this dimension quit easily in the face of frustration and have changeable moods (Cloninger et al., 1997). The negative association with NS and the positive association with RD are therefore consistent.

When comparing these associations in only the MO group, the positive associations P showed with NS3 and RD1 are no longer significant. In addition, the positive association between HA (HA and HA4) and RD4 is also non-significant. Despite the caveats regarding the inconsistency with Cloninger (1987), given the logic of these associations, it is curious that they are not significant in the migraine group. This could indicate that there are interactions between the temperament dimensions in keeping with Cloninger's theory, and,

when impacted by a disorder such as migraine, result in different presentations between groups.

The results of the study support the alternative hypothesis for research question one: MO and HA are related. This provides support for a ‘migraine personality’ of which HA is a characterising feature, the way in which HA is conceptualised in Cloninger’s theory as well as the migraine model proposed in this study. The identification of a migraine personality presentation can assist in accurate diagnoses, development of future treatments and personalised treatment plans, understanding patient behaviour and predicting treatment outcome, and incorporating personality in wellbeing and stress. These results are consistent with previous studies, although they do conflict with studies negating a relationship between MO and HA. Correlations were noted between the dimensions and subdimensions which were minimally consistent with the expectations. However, the influence of migraine on these correlations provides added support for a migraine personality profile as the results indicated that a clustering variable, such as a disease process, could result in different associations between the temperaments.

Cloninger’s theory also relates each dimension to a neurotransmitter system by which a psychological manifestation is connected to a physiological basis, and *vice versa*. The serotonergic system is purportedly associated with the HA dimension (Elovainio et al., 2004; Nelson & Cloninger, 1995, 1997) and has been considered a plausible mechanism for the involvement of HA in migraine pathophysiology (Sánchez-Román et al., 2007). Thus, the relationship between HA and serum serotonin concentration was explored.

6.3. Temperament and serum serotonin concentration

In Cloninger's theory, it was proposed that the serotonergic system underlies HA as each of the temperament dimensions are purportedly underpinned by a neurotransmitter system (Abbate-Daga et al., 2007; Montag, 2014). However, the results of the current study indicated that there were no significant correlations between the serum serotonin concentration and any of the temperament dimensions or subdimensions. Therefore, the null hypothesis is accepted: There is no correlation between temperament scores and serum serotonin concentration.

These results are dissimilar to some previous studies which have indicated a relationship between serotonin and HA (Gerra et al., 2000). There are other variables which could have influenced the relationship between neurotransmitter and temperament. In the study by Wessman et al. (2012), participants were firstly clustered according to their scores on the TCI to identify temperament patterns. The participants also completed measures of life habits, socioeconomic status, and health which were then assessed for relationships to the temperament patterns (Wessman et al., 2012). It is possible that a larger sample and clustering could have identified significant associations. For example, HA has been associated with both depression and anxiety (Ball et al., 2002; Engström et al., 2004; Knaster et al., 2012; Mochcovitch et al., 2012) which in turn are proposed to be related to serotonin (Bakar et al., 2015; Cahill et al., 2014; Cahill & Murphy, 2004; Shaik et al., 2015). Although this study included participants who had been previously diagnosed with a psychiatric disorder, no measures were included to assess anxiety and depression.

However, these results are in keeping with previous genetic studies which did not find any association between neurotransmitter gene regions and their respective temperament dimensions (Ham et al., 2004; Herbst et al., 2000; Kusumi et al., 2002; Munafò et al., 2009; Samochowiec et al., 2001; Tuominen et al., 2013), despite other studies indicating the opposite (Baeken et al., 2014; Nyman et al., 2009). Furthermore, this result is consistent with the literature disagreeing with the manner in which the relationship between these two variables is presented in Cloninger's theory. Previous literature has advocated that the one temperament to one neurotransmitter assumption is too simplistic. Zuckerman (1995) agreed with the assumption that serotonin is involved, but disagreed with no interaction at the neurotransmitter level and instead proposed that the other neurotransmitter systems as well as their hormones and enzymes are involved (Ruegg et al., 1997; Widiger et al., 2006; Zuckerman, 1995). This reasoning may relate to the lack of significant association with any of the temperament dimensions. In addition, Widiger et al. (2006) commented that it was unlikely that a temperament dimension itself, which incorporates a wide range of attributes and brain systems, would be confined to association with only one neurotransmitter. Therefore, it could be that attempts to identify such a relationship did not take into account the complexity of such a relationship. This study did not assess the concentrations of the other proposed underlying neurotransmitters in Cloninger's theory. Further studies could explore all four neurotransmitter systems as a means to investigate interactions at multiple levels.

There are also method factors in the current study which could have been influential in this null result. The normal range for serotonin concentration is 101 to 283 ng/mL (UCSF Medical Center, 2009). The range in this study was 0.0296 – 1.949 ng/mL indicating that there were extremely low levels of serotonin in the samples used. Although this is consistent

with the difficulties related to dilution of the samples during the ELISAs, this could also be an explanation as to why no significant associations were found between serotonin and migraine. In addition, and possibly relating to the small levels within the samples, the statistical calculations used to ascertain precision of the ELISAs was high. This indicates that the precision for all three of the ELISAs were low which could have been the result of several factors. This may have influenced the results. Lastly, due to the challenges regarding proper dilution of the samples, the samples had to be stored for a longer period than anticipated. They were also subjected to an additional freeze-thaw cycle which may have contributed to the null finding.

Therefore, Cloninger's theory received mixed support in this study. It has been noted that the terms used by other personality theories, including neuroticism, introversion, or inhibition, refer to traits similar in conceptualisation to HA (Brändström, 2009; Cloninger, 2008; Mardaga & Hansenne, 2007; Rettew & McKee, 2005; Smillie et al., 2006; Smillie, 2008). This commonality across theories indicates that this is a core conception in personality theory and the HA conceptualisation was also supported in this study as discussed in the previous section. However, its proposed association with the serotonin neurotransmitter was not supported and may be too simplistic a relationship and additional factors should be taken into account. There were several possible explanations identified in the literature but there were also methodological factors including low serotonin concentrations, additional freeze-thaw cycles, or imprecision which may have been influential. This is also true for the proposed migraine model. The next step was to determine if there was a relationship between migraine and serotonin concentration.

6.4. Migraine and serum serotonin concentration

The results of the current study did not indicate a significant association between serum serotonin concentration and migraine. This was an unexpected result given previous studies supporting the role of serotonin in migraine (Boz et al., 2004; Di Piero et al., 2001; Park et al., 2006), and in HA, which would have led one to expect a significant association with migraine in the current study.

The results also conflict with studies reporting a central hyposerotonergic state between migraines (Panconesi, 2008; Peterlin et al., 2009; Supronsinchai et al., 2014) and then an increase of serotonin during the attack (Panconesi, 2008). However, using serum serotonin concentration is a peripheral measure of serotonin, rather than a central measure. With regards to peripheral studies, previous research has largely indicated normal platelet and plasma serotonin concentrations both interictally and during migraine attacks for MO patients and controls (Panconesi, 2008), although Di Piero et al. (2001) reported the same findings as those reported above for central serotonin concentration. Further, Panconesi (2008) states that studies using peripheral measures of serotonin were often inconsistent as a result of both negative results and confounding variables. Therefore, using a peripheral measure may have contributed to the results of the current study.

This study did not support an association between either MO or HA and serum serotonin concentrations which thus contradicted the proposed migraine model. However, this could have occurred for several reasons related to the model itself, the method challenges discussed in the previous section, or using a peripheral rather than central measure of

serotonin concentration. Therefore, it remained plausible that migraine and HA are underpinned by the serotonergic system but in a more complex manner than proposed here.

6.5. Recommendations for future research

Due to the extremely low serotonin levels in the participant samples, it is recommended that further studies be performed which compare the use of central and peripheral measures of serotonin. In addition, further research is required to establish normative values not only for the South African migraine population, but also with regards to the South African population as a whole. Not only would this be beneficial to studies using serotonin concentration, but it would also be important in determining the most accurate laboratory procedures for measurement.

The TPQ and various other personality tests should be normalised for a South African population. This would provide a reference for future studies in migraine and in other personality studies. Furthermore, a larger study to explore these questionnaires in the migraine population would be important as there were interesting temperament results and interactions identified in this study with regards to the MO group. A larger study and reference values would assist in reproducing these results and performing a comparison on an international level.

The results of this study provided indications of a relationship between migraine and HA but not between either migraine or HA with serotonin concentration. However, it is probable that these relationships are more complicated than what was proposed and therefore much research is needed. This includes development of personality profiles, the association

of these profiles with a wide variety of health, life habits, and wellbeing, involvement of depression and anxiety with migraine in the South African population, as well as a longitudinal study to determine the effects of chronic pain on personality.

Furthermore, the one-to-one association between each temperament dimension and a particular neurotransmitter system proposed in Cloninger's theory did not receive support in this study. Therefore, further research is required with a larger sample, assessment of all four neurotransmitter systems, and correcting for the method difficulties encountered in this study.

6.6. Recommendations for practical application

There are various treatments available to migraine sufferers. However, it was indicated in this study that MO is related to HA. Personality traits typical of this temperament may lead to emotional and cognitive changes influencing both the perception and experience of pain; a vicious cycle. As Gustin et al. (2015) note, it could therefore benefit those receiving treatment programs for a trait-focused therapy aspect to be included, specifically, a focus on HA. This proposal is also supported by Sánchez-Román et al. (2007) who reported that the personality of individuals with chronic pain can alter some personality traits through, as an example, psychological therapy (Gustin et al., 2016; Sánchez-Román et al., 2007). The results of this study therefore contribute towards a psychobiological perspective of migraine which takes personality into consideration. This could also provide additional information to migraineurs, doctors, and therapists regarding the nature and extent of migraine consequences. Future research, treatment, and treatment plans could thus have a more holistic viewpoint.

As recommended in the previous section, further explorations are indicated into several factors which may identify relationships between personality, migraine, and anxiety and depression. In the future, this research and branches from it may assist with the clinical treatment of individuals as well as lead to a better understanding of individual behaviour.

6.7. Limitations and contributions

There were several limitations of the current study:

1) The sample size may have been insufficient to detect a meaningful difference with regards to serotonin concentration both within and between groups or to generalise to the general migraine population: A relatively small cohort of participants was used and the sample was migraine patients without aura. Both of these factors limit the external validity of the results. The sample may not be large enough to accurately reflect the general migraine patient population.

2) There were strict inclusion criteria, nonparticipation bias and obstacles limiting access. In addition, most participants were white, female, had a tertiary education and spoke English as a first language which limits the generalisability of the results. Additional threats to validity may be present when considering nonparticipation bias and the geographic or cultural characteristics of the population from whence the sample was selected (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley III, 2009). Most of the participants had European heritage and were most often English-speaking, female, employed, and held a tertiary education in both the migraine and control groups. The conclusions drawn regarding the association between neurotransmitter concentrations and temperament dimensions are

therefore not absolute and will need to be further explored in a more representative sample (Celikel et al., 2009).

3) The TPQ is a self-report questionnaire which was completed online by the participants and therefore subject to inaccuracies, response bias, and cultural interpretation. Asking individuals to rate themselves with regards to their preferences and behaviours is a commonly used method in personality psychology and has several advantages. Individuals are considered to know more about and be more willing to talk about themselves. Scoring the results of personality questionnaires is uncomplicated if validity and reliability of the assessment measure has been established, and the process of administration is considered relatively inexpensive and quick (McDonald, 2008). However, there are also disadvantages of using self-report data. Although the TPQ has been shown to have adequate validity and reliability, retrospective self-reports can be distorted by memory, summarization processes both during memorization and during recall to complete the questionnaire, or the current state of the participant whilst they complete the questionnaire (Stone & Shiffman, 2002). With regard to personality questionnaires, there is also the influence of 'response biases' where the participant responds to the questions based on factors unrelated to the content of the question. For example, the participant could want to be viewed in a more favourable light. There is also the theory that the participant is not actively seeking to be seen more positively, but that they themselves have a distorted view of self which leads them to answer the items in a self-enhancing manner. These potential biases could destroy the validity of the personality questionnaire (McDonald, 2008). Although the participants were able to complete the questionnaires in their own time and space in order to give them a safe environment to fill in the questionnaires at their leisure, cognitive influences may have an impact on the results of the current study. Cultural influences on item interpretation must also be acknowledged as an

influence (McDonald, 2008). The participants may also have been deterred by the blood donation aspect or the requirement for Internet access.

4) A non-experimental correlational design was used. Studies using this design cannot manipulate the variables used, and therefore causality can only be suggested and not identified. The limitation this holds for the study is that any relationship identified between a given temperament dimension and neurotransmitter concentration could be caused by a third variable. Matching was used in the study in order to prevent this as much as possible. Also, random assignment of the participants was not possible in this study which further limits external validity (Johnson, 2001). Lastly, this sample was cross-sectional. This implies that there could be no additional information regarding the development of either migraine symptoms or temperament provided by this sample. Migraine may be associated to temperament, particularly HA, for a variety of reasons and the possible influence of one on the other may involve complex, non-linear interactions between numbers of factors. These factors may include the serotonergic neurotransmitter system but any speculations drawn in this study concerning this potential mechanism are hypothetical and require further investigation with longitudinal studies (Kristensen et al., 2009).

5) The ELISA method used in this study was imprecise. There were several challenges which occurred during the laboratory work which extended the process. This may have had an impact on the results obtained as the samples not only had to be stored for a longer period but also had an additional freeze-thaw cycle. However, the latter was unavoidable as requesting an additional blood donation was not an option.

The results of the current study provide valuable contributions in four ways: 1) support for and disagreement with Cloninger's Psychobiological Theory of Personality; 2) addition to the literature regarding the use of Cloninger's theory and the TPQ in South Africa; 3) support for a 'migraine personality' characterised by HA; and 4) a psychological perspective of migraine which could assist in future treatments.

The study results separated the MO and control groups in a predictable manner and thereby the conceptualisation and construct validity of HA in Cloninger's Psychobiological Theory of Personality was supported. The results also showed several interactions between the temperament dimensions and subdimensions which were theorized by Cloninger. Not only does this add to the general body of research regarding Cloninger's theory, but it adds to the limited explorations using this theory and the TPQ as an assessment measure in a South African population.

The study also added to the research revolving around this theory as it disagreed with several facets as well. The interactions between temperament dimensions and subdimensions alluded to above also did not show some expected relationships, but did reveal some which were unexpected. Lastly, the results did not find a significant relationship between the HA temperament and serum serotonin concentration. Although there could have been method factors related to this null finding, it remains an area of contention. This provides beneficial topics for debate as well as avenues for further research as it may be unique to the South African general or migraine population.

There has been much debate regarding the relationship between migraine and HA. This study therefore contributed to this debate in a meaningful manner and also supported the

literature indicating that there is such a relationship by portraying a ‘migraine personality’. Furthermore, this is one of the first studies to explore migraine using a personality theory in South Africa. Not only does this contribute in an academic sense, but it also assists in paving the way for a different perspective of migraine treatment which may lead to new and effective therapies.

6.8. Conclusion of the study

This study explored three possible relationships: MO and HA; HA and serotonin; and MO and serotonin. Following univariate analyses, the results suggested that MO patients have a distinct temperament profile when compared to control participants. MO patients were characterised by a high HA score. Although a one-to-one relationship was proposed by Cloninger, this study did not provide support for a relationship between HA and serotonin. The study also did not report a significant association between MO and serotonin, and therefore could not establish that this neurotransmitter plays a central role in a migraine model. These negative findings are supported by some previous studies, but could also have occurred due to several limitations of the study including small sample size and method challenges. Following consideration of the current scholarship, it is also plausible that the suggested relationships were posed in too simplistic a manner and that the incorporation of other factors, such as anxiety and depression, could illustrate a more complete model which takes into account the complexities of the systems involved in migraine.

The indicated relationship between MO and HA supports the role of personality in the pain behaviour of migraine patients. Their personality profile could therefore assist in the treatment of migraineurs through its incorporation in their treatment approach and plan. Due

to the debilitating effect of migraine on all areas of life, this is considered a significant consideration that warrants attention from those assisting South Africa's numerous migraine without aura patients.

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APPENDIX 1

Please read the instructions carefully before answering the questions. Answer as honestly as possible, by placing an X in the box with the answer that is best for you.

The following questions are all about headaches. Please answer all the questions.

Has headache limited your activities for a day or more in the last three months?		1. yes			2. no						
Are you nauseated or sick to your stomach when you have a headache?		1. yes			2. no						
Does light bother you when you have a headache?		1. yes			2. no						
If you are experiencing a headache now, how painful is it?	No headache now	Mild							Severe		
		1	2	3	4	5	6	7	8	9	10
How often do you experience headaches in a month? Please answer with a number, e.g. 2 for twice											
How long do these headaches usually last?	1. less than 2 hours	2. 3 to 4 hours	3. 5 to 12 hours	4. 12 to 24 hours	5. several days	6. 1 week or longer					
How painful are these headaches on average?		Mild							Severe		
		1	2	3	4	5	6	7	8	9	10
Please mark all the types of pain you experience with these headaches	1. Throbbing / pounding	2. Dull ache	3. Pressure	4. Sharp pain	5. Other (describe):						

Where do you feel the headache pain? Mark all of the relevant areas	1. behind my right eye	2. behind my left eye	3. right temple	4. left temple	5. above my right eyebrow
	6. above my left eyebrow	7. at the top of my head	8. at the back of my head on the right	9. at the back of my head on the left	
How old were you when the headache started?					
How many days of work/school/studies do you miss in a year because of your headaches?					
What symptoms do you experience during a headache? You may mark as many as you experience	1. Nausea	2. Vomiting	3. Light sensitivity	4. Dizziness	
	5. Numbness	6. Tingling of the arms or legs	7. Ringing in the ears	8. Irritability	
	9. Blurred vision	10. Slurred speech	11. Puffy eyelids	12. Teary eyes	
	13. Difficulty concentrating	14. Runny nose	15. Diarrhoea	16. Drooping eyelid	
	17. Loss of vision	18. Muscle weakness	19. Loss of consciousness	20. Facial sweating	
	21. Seeing flashing lights	22. Feeling lightheaded	23. Other? Specify:		