Transdiagnostic Compulsive Behaviour: A Multidimensional Investigation into the Affective Processes underlying Maladaptive Repetitive Behaviours.

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List of abbreviations

AAQ	Acceptance and Action Questionnaire
ACC	Anterior Cingulate Cortex
ACT	Acceptance and Commitment Therapy
ANOVA	Analysis of Variance
AUCi	Area Under the Curve
BIC	Bayesian Information Criterion;
BF	Bates Factor
BOLD	Blood Oxygen Level Dependent
CAR	Cortisol Awakening Response
CBT	Cognitive Behavioural Therapy
CESD	Centre for Epidemiologic Studies Depression Scale
CFI	Comparative Fit Index
CNA	Compulsive Non-Avoidant Subgroup
CR	Compulsive Reactive Subgroup
CS	Compulsive Stressed Subgroup
CSF	Corticospinal Fluid
CSTC	Cortical-Striatal-Thalamic-Cortical
DBT	Dialectical Behavioural Therapy
dl	Dorsolateral
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual
EA	Experiential Avoidance
EEG	Electroencephalogram
GAD-7	General Anxiety Disorder 7-item questionnaire

GLM	General Linear Model
ICD	International Classification of Diseases
IFG	Inferior Frontal Gyrus
IUC	Intolerance of Uncertainty
fMRI	Functional Magnetic Resonance Imaging
HPA	Hypothalamic-pituitary-adrenal axis
MANOVA	Multivariate analysis of variance
MBCT	Mindfulness based cognitive therapy
MEAQ	Multidimensional experiential voidance questionnaire
MEAQ-BA	Multidimensional experiential voidance questionnaire behavioural avoidance subscale
MnInc	Mean increase
mPFC	Medial prefrontal cortex
NAC	Nucleus Accumbens
OCD	Obsessive Compulsive Disorder
OC	Obsessive Compulsive
OFC	Orbitofrontal Cortex
PFC	Prefrontal Cortex
PHQ-9	Patient health questionnaire 9-item
PSS	Perceived stress scale
PTSD	Post-traumatic stress disorder
RDoC	Research Domain Criteria
RMSEA	Root Mean Square Error of Approximation
rs-FC	Resting-state Functional Connectivity
SEM	Structural Equation Modelling

SPL	Superior Parietal Lobe
SRMR	Standardized Root Mean Square Residual
SRI	Serotonin reuptake inhibitor
STAI-Y2	State-trait anxiety subscale version Y2
UPPS	Impulsive behaviour scale
vlPFC	ventrolateral Prefrontal Cortex
Y-BOCS	Yale-Brown Obsessive Compulsive subscale

Context of Research

This thesis forms the major research component of the Doctorate of Clinical Neuropsychology program at Monash University, Melbourne Australia. This is a four-year combined clinical training and research program. This thesis was conducted at BrainPark, The Turner Institute for Brain and Mental Health, School of Psychological Sciences and Monash Biomedical Imaging Facility.

The current thesis was undertaken as part of the "Conquering Compulsions" Research Trial (Clinical Trials ID: NCT03067636). This is an 8-week longitudinal follow-up exercise and stress management intervention for individuals with transdiagnostic compulsive behaviours. The trials chief investigators included my supervisors Prof. Murat Yucel and Dr. Rebecca Segrave. At the time of commencing my dissertation, Conquering Compulsions had an established set of study aims and objectives, as outlined in their ethics approved study protocol (Monash University Human Research Ethics Project ID: 0437). In collaboration with my supervisors, I developed a thesis topic and unique set of aims that complemented the larger study. I incorporated pre-existing study measures and introduced additional measures specific to the current thesis aims. To meet these unique aims, further data collection was also required outside of what was being collected as part of the trial. This additional protocol was also approved by Monash University Human Research Ethics (Approval Number 8239).

Although this dissertation utilises cross-sectional data from the trial, obtained from the baseline assessment prior to any intervention, I was heavily involved in the trial itself and responsible for key elements related to trial design, implementation, data collection and analysis. With respect to the measures utilised in the current thesis, I was responsible for

measure selection, protocol design, data collection, analysis and interpretation. This included protocol design associated with the collection and analysis of biological samples. My supervisors provided guidance throughout this process and other members of the research team assisted with data collection. My supervisor Dr. Chao Suo provided considerable assistance with regards to the magnetic resonance imaging, completing the pre-processing and providing advice relating to analysis. I prepared each manuscript under the guidance of my supervisors, receiving additional input from other collaborators.

In line with the Monash University guidelines, chapters are presented in a 'thesis by publication' format, in which parts of the chapters have been written as manuscripts and submitted for publication. As such, there is some repetition of information across chapters.

The thesis starts with an overview of the thesis structure (Chapter 1), followed by a detailed review of the literature that informed the research investigations (Chapters 2 – 5). Chapters 6 and 7 contain two prepared manuscripts which address the main aims of the thesis. Regarding publication status, Chapter 6 entitled "The role of Experiential Avoidance in Transdiagnostic Compulsive Behavior: A Structural Model Analysis" has been accepted for publication with the Journal of Addictive Behaviors (published in May 2020). Chapter 7, entitled "Transdiagnostic Phenotypes of Compulsive Behavior and Associations with Psychological, Cognitive and Neurobiological Affective Processing" was submitted to the Journal of Translational Psychiatry on 2nd June 2020 and remains under review. Finally, Chapter 8 summarises the thesis findings and provides a general discussion of the contribution of this work. Limitations and future research recommendations are also provided.

Abstract

Traditional classification systems, such as the Diagnostic and Statistics Manual (DSM), remain the primary means for classifying psychopathology despite considerable evidence showing diagnostic categories are not valid representations of the underlying pathology. For this reason, researchers are now adopting a transdiagnostic research approach, focusing on maladaptive behavioural functions that span across disorders, as well as neural circuits and their constituent components.

Compulsivity is a transdiagnostic construct which has received considerable interest in recent years. It is defined by rigid, repetitive, and functionally impairing behaviors and is thought to underlie multiple disorders, including obsessive-compulsive disorder, substance and behavioural addictions. Despite identification of shared psychological, cognitive and neurobiological underpinnings, the causes of compulsive behaviour remain poorly understood. Compulsive behaviours have traditionally been examined in the context of specific diagnostic categories or rely on one or two laboratory measures (e.g. self-report, cognitive task, brain imaging) to explain phenotypic variance. This approach is unlikely to capture complex psychiatric behaviour, calling for integrated, multidimensional research, examining how different combinations of disruptions across multiple measures influence behaviour.

To date, the contribution of affect in compulsive behaviour has been largely overlooked. Thus, the overall aim of the thesis was to identify and understand the various affect-related processes which may cause or maintain compulsive behaviour. Two research investigations were conducted to achieve this aim. The first study investigated if there was a relationship between the psychological affective process Experiential Avoidance (EA), an unwillingness to tolerate negative internal experiences, and the frequency and severity of transdiagnostic compulsive behaviours. A large sample (*N* = 469) of community-based adults completed

online self-report questionnaires measuring EA, psychological distress and the severity of seven obsessive-compulsive and addiction-related behaviours. Structural equation modelling was used to delineate the relationship between EA and compulsive behaviour.

The second study drew on a heterogenous sample of adults (*N* = 45) exhibiting compulsive behavioural patterns in alcohol use, eating, cleaning, checking or symmetry. This study expanded on study one by integrating additional cognitive and neurobiological measures with psychological self-report measures of EA and distress. Study two aimed to determine if dysfunction across *multiple* dimensions (or measures) could explain compulsive behaviour and thus, if shared affective processing disruptions might underpin transdiagnostic compulsivity. Data-driven statistical modelling of multidimensional markers encompassing psychology (i.e. EA and distress), cognition (i.e. valence learning computer task) and neurobiology (i.e. cortisol awakening response) were utilized to identify homogeneous subtypes that were independent of traditional clinical phenomenology. The neurobiological validity of the subtypes was assessed using functional magnetic resonance imaging (i.e. amygdala resting-state connectivity).

The aims of the thesis were achieved. Findings from the first study revealed a high portion of compulsive behaviours may be conceptualised as maladaptive attempts to regulate distressing emotions. In the second study, three neurobiologically distinct subtypes were found, independent of the type of compulsive behaviour (i.e. obsessive-compulsive, addiction-related) and were instead based on multidimensional markers of affective processes. Consideration of subtype profiles offered new insights into how different affective systems interact and influence the expression of compulsive behaviour. Overall, the current thesis has generated new understandings of the underlying causes of compulsive behaviour. Importantly, both investigations were consistent with the new and emerging reconceptualization of mental health disorders.

General declaration

Monash University Declaration for thesis based or partially based on conjointly published or unpublished work.

In accordance with Monash University Doctorate Regulation 17.2 Doctor of Philosophy and Research Master's regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes an original paper accepted for publication in a peer-reviewed journal and an original paper under review in a peer-reviewed journal. The core theme of the thesis is affective processing in transdiagnostic compulsive behaviour. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within BrainPark, The Turner Institute for Brain and Mental Health, School of Psychological Sciences and Monash Biomedical Imaging Facility under the supervision of Prof. Murat Yücel, Dr Rebecca Segrave and Dr. Chao Suo.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers across multiple sites and acknowledges input into team-based research.

In the case of chapters six and seven, my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s)	Nature and % of Co-author's contribution*	Monash student co-author
Six	The role of Experiential Avoidance in Transdiagnostic Compulsive Behavior: A Structural Model Analysis.	Published in the Journal of Addictive Behaviors	Lauren Den Ouden; Conceptualisation of the study, development of the protocol, recruitment of participants, execution of experiments, analysis of data and preparation of manuscript; 80%	Jeggan Tiego	Data curation, Formal analysis, Writing - review & editing; 7.5%	No
				Rico Lee	Conceptualization, Protocol development and administration, Writing - review & editing; Collective 5%	No
				Lucy Albertella	Protocol development and administration, Data curation, Writing - review & editing; Collective 5%	No
				Lisa-Marie Greenwood	Protocol development and administration, Data curation, Writing - review & editing; Collective 5%	No
				Leonardo Fontenelle	Conceptualization, Writing - review & editing; Collective 5%	No
				Murat Yücel	Conceptualization, Funding Acquisition, Writing - review & editing; Collective 5%	No
				Rebecca Segrave	Conceptualization, Protocol development and administration, Funding Acquisition, Writing - review & editing; 7.5%	No
Seven	Transdiagnostic Phenotypes of Compulsive Behavior and Associations with Psychological, Cognitive and Neurobiological Affective Processing	Under review Journal of Translational Psychiatry	Lauren Den Ouden; Conceptualisation of the study, development of the protocol, recruitment of participants, execution of experiments, analysis of data and preparation of manuscript; 70%	Chao Suo	Conceptualization, Protocol development and administration, Data curation, Formal analysis, Writing - review & editing; 10%	No
				Lucy Albertella	Conceptualization, Protocol development and administration, recruitment of participants, execution of experiments, Writing -	No

					review & editing; Collective 5%	
				Lisa-Marie Greenwood	Conceptualization, Protocol development and administration, recruitment of participants, execution of experiments, Writing - review & editing; Collective 5%	No
				Rico Lee	Conceptualization, Writing - review & editing; Collective 5%	No
				Leonardo Fontenelle	Conceptualization, Writing - review & editing; Collective 5%	No
				Jeggan Tiego	Formal analysis, Writing - review & editing; Collective 5%	No
				Linden Parkes	Conceptualization, Writing - review & editing; Collective 5%	No
				Sam Chamberlain	Conceptualization, Writing - review & editing; Collective 5%	No
				Karyn Richardson	Writing - review & editing; Collective 5%	No
				Rebecca Segrave	Conceptualization, Protocol development and administration, Funding Acquisition, Writing - review & editing; 7.5%	No
				Murat Yücel	Conceptualization, Protocol development and administration, Funding Acquisition, Writing - review & editing; 7.5%	No

I have not renumbered sections of submitted or published papers.

Student name: Lauren Den Ouden

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Murat Yücel

Publications during enrolment

The following publications and presentations arose from research conducted during my doctoral candidature.

Publications

1. Den Ouden, L., Tiego, J., Lee, R.S.C., Albertella, L., Greenwood, L., Fontenelle, L.F., Yucel, M., & Segrave, R. (2020). The role of Experiential Avoidance in Transdiagnostic Compulsive Behavior: A Structural Model Analysis. Addictive Behaviors. 108. 106464. doi: 10.1016/j.addbeh.2020.106464
2. Den Ouden, L., Suo, C., Albertella, L., Greenwood, L., Lee, R.S.C., Fontenelle, L.F., Parkes, L., Tiego, J., Chamberlain, S.R., Richardson, K., Segrave, R., & Yucel, M. (2020). Transdiagnostic Phenotypes of Compulsive Behavior and Associations with Psychological, Cognitive and Neurobiological Affective Processing. Translational Psychiatry (under review)

Conference Proceedings

- Den Ouden L, Lee RC, Tiego J, Albertella L, Segave RA, & Yücel M. Experiential avoidance as a driving factor behind compulsive behaviour. *Society for Mental Health Research* (Oral Presentation), Noosa, Australia. November 2018.
- Den Ouden L, Lee RC, Tiego J, Albertella L, Segave RA, & Yücel M. Experiential avoidance as a transdiagnostic factor driving compulsive behaviour: Structural Model Analysis. *9th World Congress of Behavioral and Cognitive Therapies* (Oral Presentation), Berlin, Germany. July 2019.
- Den Ouden L, Suo C, Albertella L, Greenwood L, Parkes L, Tiego J, Segrave R & Yücel M. Can we identify Transdiagnostic Subtypes within Compulsive Disorders? *College of Clinical Neuropsychologists* (Oral Presentation), Barossa Valley, Adelaide. November 2019.

- Den Ouden L, Suo C, Albertella L, Greenwood L, Parkes L, Tiego J, Segrave R & Yücel M. Can we identify Transdiagnostic Subtypes within Compulsive Disorders? *Society for Mental Health Research* (Oral Presentation), Melbourne, Victoria. November 2019.

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To my co-authors and collaborators, thank you for all the time you spent helping me improve my work and develop as a researcher. I am grateful to have had the opportunity to work with each of you and hope to have collaboration opportunities again in the future. A special thank you to Doctor Lucy Albertella, Doctor Lisa-Marie Greenwood and Jeggan Tiego who were incredibly generous with their time throughout this process and always lent a supportive ear.

I would also like to thank the Doctoral teaching staff for their passion and dedication developing the clinical component of this degree. I have thoroughly enjoyed the program and feel fortunate to have experienced such a high standard of clinical training.

To my family and friends, thank you for your patience, unconditional love and support throughout this process. I can't tell you how important the regular check-ins, gentle encouragements and fun nights were in getting me through. I am so lucky to have you all in my life.

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CHAPTER ONE

1. Thesis Outline

Obsessive-compulsive disorder (OCD), substance addiction and non-drug related behavioural addictions, such as pathological gambling, affect a significant proportion of the population, regardless of gender and culture, have an early age of onset with a prolonged course and are associated with reduced quality of life and the development of marked psychiatric comorbidities. Moreover, majority of individuals with obsessive-compulsive and addiction-related behaviours are not in clinical care, with between 60-78% of individuals never seeking treatment – the highest rates of any mental health disorder - or are exhibiting problematic behaviour at a subclinical level. Early and chronic trajectories, as well as poor treatment outcomes highlight that our current understanding of what causes OCD and addictive behaviours is underdeveloped. In order to improve patient outcomes and design more effective interventions we must have knowledge of the basic underlying processes contributing to disorder presentation. The prevalence of subclinical individuals emphasizes the need to understand the processes involved in the early stages of psychopathology, where there is opportunity to implement early treatment interventions.

Although still in its nascent stage, research is beginning to map common psychological, cognitive and neurobiological underpinnings of traditionally distinct disorders such as OCD and addiction - an essential step forward in developing more effective, personalised treatments. The current thesis focusses on *Compulsivity,* an underlying, intermediate phenotype which can explain many rigid, repetitive and functionally impairing behaviours. Rather than being conceptualised as categorically distinct, behaviours like addiction, OCD, binge-eating and gambling are now being viewed as different manifestations of the same compulsivity-related etiological processes. This is exciting as it opens the possibility to

generate new understandings of previously enigmatic mental health disorders. However, compulsivity is a highly complex and multifaceted construct, and current knowledge of how it should be operationalized and the processes contributing to its development and maintenance is limited.

The current thesis, designed to build upon this knowledge, focusses on the relationship between transdiagnostic compulsive behaviour and Experiential Avoidance (EA), a poor affect regulation strategy driven by a psychological unwillingness to tolerate negative affective states. Several frameworks of understanding have been posited to explain compulsive behaviour; however, models of EA have received relatively little attention in the research literature. This is despite good evidence and reasoning to suggest that compulsive behaviour may be the product of maladaptive attempts to avoid uncomfortable affective states.

As such, I sought to determine if transdiagnostic compulsive behaviour could be explained in the context of EA and related maladaptive affective processes. The current series of studies began by attempting to establish a direct link between EA and compulsive behaviour, and thus determine whether compulsive behaviour may be conceptualised as a poor attempt to avoid negative affective states. The second study sought to extend on the first by identifying cognitive and neurobiological affect processing systems, including EA, that may underlie the relationship between maladaptive affective processing and compulsive behaviour.

The following studies were conducted to achieve these aims:

1. A study examining the nature of the relationship between EA and transdiagnostic compulsive behaviour, using structural equation modelling.

2. A studying identifying if naturally occurring transdiagnostic phenotypes of compulsive behaviour existed, using measures of affective processing. This was done using data-driven clustering to detect “hidden” subtypes based on different combinations of compulsivity and affective processing. The validity of subtypes was assessed using functional brain imaging.

The thesis contains three major parts and is presented in the following format:

The first part is the literature review, which is divided into four chapters (Chapters 2 - 5) and aims to introduce the reader to the concept of transdiagnostic, multidimensional research and how this can be applied to compulsive behaviour (Chapter 2). The clinical characteristics of the various disorders that fall under compulsive behaviour are described, as well as the current understandings of their psychological, cognitive and neurobiological causes (Chapter 3). I then focus on one particular model for understanding compulsive behaviour: Experiential Avoidance (Chapter 4). Using Experiential Avoidance as a framework for understanding compulsive behaviour, I next discuss the cognitive and affective measures tightly linked to processes relevant for compulsivity, that may further current understanding of the systems driving compulsive behaviour (Chapter 5).

The second part (Chapters 6 - 7) contains two research studies that bring insight into psychological, cognitive and neurobiological correlates of compulsive behaviour. In the first study, I establish a link between Experiential Avoidance, distress and transdiagnostic compulsive behaviour. In the second study, several seemingly heterogeneous compulsive behaviours are reclassified according to markers of known relevance to affect processing and compulsivity. The reclassified subgroups are then validated using resting-state functional brain imaging. The first study has been accepted to the Journal of Addictive Behaviors, and the second under review at the Journal of Translational Psychiatry

(submitted to the journal on 8th June 2020). Both studies are presented in the submission format.

The third and last part of the thesis (Chapter 8), aims to integrate the results of the two studies into the current understanding of transdiagnostic compulsivity. The main highlights from the two studies and their contribution to models for understanding compulsivity are discussed. The results are compared to the existing literature. I end the thesis describing the achievements, limitations and potential future work.

CHAPTER TWO

2. A transdiagnostic approach to understanding compulsive behaviour

2.1. Traditional approaches to the study of mental health

The DSM approach to mental health disorders: Worldwide, classification systems are used to aid the diagnosis of disorders and diseases. The DSM is one of the most widely used diagnostic tools for the classification of mental health disorders (Evans et al., 2013; First et al., 2014). In clinical practice, it is used to guide diagnosis and treatment planning. In research, it is the standard system used to obtain research grants regarding disorder aetiology and conduct treatment intervention trials. By and large, the DSM is the framework within which we treat and understand mental illness.

More recently however, the validity of the DSM diagnostic system has been called into question (Lilienfeld, Smith, & Watts, 2013). The DSM groups mental health disorders into similar categories based on observable behaviours and overt symptoms. These categories are determined based on a Task Force consensus vote, therefore relying on descriptive psychiatry as opposed to empirically-based research evidence. Moreover, what constitutes a 'disorder' changes each time the Task Force meets to revise a new version of the DSM. This approach is drastically different from all other areas of medicine, which rely on objective evidence of disorder, based on findings from research science.

It is therefore unsurprising that the mental health profession remains plagued by high levels of disease burden and poor patient outcomes. In a 2013 publication in BMC medicine, Dr. Bruce Cuthbert and Dr. Tom Insel, both former directors of the National Institute for Mental Health (NIMH), stated that in comparison to other medical professions, the mental health field has lacked progress. This was evidenced by unchanging mortality and prevalence rates across all mental illnesses, lack of clinical tests for early detection of

pathology, and absence of well-developed preventative interventions (Cuthbert & Insel, 2013).

Although the complicated nature of the brain contributes to our underdeveloped understanding of mental illness, categorical classification systems like the DSM are now recognised as impediments to progress (Lilienfeld et al., 2013). There is excessive co-morbidity between disorders that are supposedly categorically distinct (Cramer, Waldorp, van der Maas, & Borsboom, 2010), marked heterogeneity within diagnoses (Lilienfeld et al., 2013) and poor capacity for disorder categories to map onto findings from genetics and neuroscience (Hyman, 2007). This has contributed to difficulties translating basic research findings into clinical practice (Insel, 2013).

2.2. A new approach to the study of mental health: The RDoC initiative

Against this backdrop, the NIMH announced the Research Domain Criteria (RDoC) initiative. This initiative seeks to revolutionise traditional psychiatry by building a framework for understanding mental illness, grounded in findings from functional domains, including neuroscience, behaviour, cognition, genetics and physiology. It considers mental illness from a transdiagnostic point of view and rather than base diagnoses on symptoms, it conceptualizes mental disorders as disorders of brain circuitry.

RDoC provides researchers with an explicit rubric to guide research investigations, that is dynamic and constantly updated based on new research (Cuthbert, 2014). On the vertical axis are five broad domains that correspond to brain-based circuits relevant is psychopathology (i.e. negative valence systems, positive valence systems, cognitive systems, systems for social processing and arousal/regulatory systems). Within each domain are subordinate constructs that are thought to be particularly relevant to each domain (e.g. reward learning is a subordinate construct of positive valence systems domain). The horizontal axis “Units of Analysis” identifies the areas of basic science that could be used as

classes of measurement to investigate the constructs (e.g. cells, circuits, physiology, self-report, paradigms). The aim is for researchers to adapt and fill cells in the matrix to build a cohesive understanding of both mental illness and health, and how to best measure them.

In comparison to the DSM, there are several positive changes that come with this new approach. Firstly, RDoC adopts a bottom-up approach, starting with basic science (i.e. genetics, neurocircuitry, physiology) and working upwards, putting emphasis on understanding the fundamental mechanisms that result in differing degrees of dysfunction. Secondly, it aims to study the full range of mental functioning, from abnormal to normal. This means that individuals with mild or subclinical psychopathology, who do not meet diagnostic criteria, will no longer be overlooked in research. Finally, it places equal weight on behavioural functions, as well as neural circuits and their cognitive substrates. Thus, grounding dysfunction in underlying neurobiology.

Overall, the RDoC initiative offers a platform for advancing psychiatric research. It focuses on the underlying dimensions of pathology that cut across disorders, rather than reducing them to specific clusters of syndromes that may not be a valid representation of underlying aetiology. Though it is still far from completion, it is a welcome step in a new direction and seems likely to generate new understandings regarding the relationship between the brain and mental illness. In line with the RDoC initiative, the current thesis will apply a transdiagnostic, multidimensional approach to studying compulsive behaviour. However, this approach is associated with inherent strengths and weaknesses and it is important to take this into consideration. Therefore, before moving on to the focus of this thesis, the promises and pitfalls of transdiagnostic research will be considered.

2.3. The promises and pitfalls of transdiagnostic research

One of the main challenges associated with conducting transdiagnostic research is that it is difficult to define what is normal and abnormal. The DSM approach came with very

clear diagnostic categories and it was relatively simple to differentiate individuals who were with or without psychopathology. From a transdiagnostic perspective, psychopathology is viewed as continuous rather than discrete and there is a full range of symptom severity, spanning from non-existent to severe (Cuthbert & Insel, 2013). Though most agree with this continuous approach (Krueger & Markon, 2006; Markon, Chmielewski, & Miller, 2011), the seemingly simple question of "what is psychopathology?" becomes considerably more challenging as it becomes difficult to identify points along the continuum that signify meaningful transitions to more severe behaviour. This can have ramifications for research where it is necessary to have "cut-points" to define behaviour inclusion or exclusion criteria.

The current thesis faced this challenge when defining what constituted compulsive behaviour, as there were no measures available which adequately captured compulsivity across a variety of behaviours. To deal with this issue, it is recommended researchers recruit participants whose problem behaviour is above a pre-defined "tipping point" (Cuthbert & Insel, 2013). A tipping point refers to point along a continuum where small incremental changes have become significant enough to bypass a threshold and transition into more severe pathology or behaviour. This approach is particularly useful when trying to demarcate levels of severity of a behaviour along a continuous spectrum, such as mild, moderate or severe. However, it is a relatively new approach and until sufficient research base is built up, researchers must select reasonable but relatively arbitrary cut-off points.

Another challenge of transdiagnostic research is that it is difficult to define the neurobiological outcome measures that should be used. When testing the utility of an intervention, it is generally considered successful if the severity or incidence of a disorder was reduced. However, RDoC encourages researchers to move away from using diagnostic status as an indicator of psychopathology and shift towards neurobiological constructs that are markers of mental illness/health to inform intervention success. For example, higher

ventral striatum activity is related to addictive behaviour (Figee et al., 2016), therefore reduced ventral striatum activity may be a marker of treatment intervention success. This raises an issue, as many neurobiological measures do not have clear thresholds (or tipping points) for what marks normal versus abnormal and our understanding of the various indicators involved in many mental health disorders is still developing.

This emphasises the need for multidimensional, cross-sectional research to determine if certain measures are related to increased severity of target pathology and can be used as objective markers of that pathology. This can then inform treatment intervention success at the neurobiological level. It is important for measures to relate to underlying etiological mechanisms implicated in the development and maintenance of psychopathology. This is particularly relevant for transdiagnostic research because different forms of pathology often share underlying processes (e.g. punishment attentional biases contribute to both depression and anxiety; Lichtenstein-Vidne et al., 2016).

Overall, there is good reason to move away from traditional classification systems, such as the DSM, and move towards transdiagnostic approach to understanding mental illness. The RDoC initiative is a useful platform to enable this movement, encouraging researchers to adopt a multidimensional approach when investigating maladaptive behaviours. This will promote a more sophisticated understanding of the psychology, cognition and neurobiology behind mental illness, inform best treatment practices and offer objective ways to track how a treatment intervention alters the fundamental mechanisms behind dysfunction.

2.4. Compulsivity: A transdiagnostic maladaptive behaviour

Compulsivity is recognised as a core feature of several debilitating mental illnesses, including obsessive-compulsive disorder (OCD), substance-use disorders, and gambling disorder. Compulsive behaviours are defined as repetitive acts characterized by a loss of

control and the feeling that one 'has to' perform them, despite an awareness that it conflicts with long term goals (Luigjes et al., 2019). They are engaged in because of their rewarding properties or to relieve anxiety or stress, even if the behaviour is inappropriate to the context and is causing functional impairment (Fineberg et al., 2010; Torregrossa, Quinn, & Taylor, 2008). Thus, there is a preoccupation or 'wanting' to perform the behaviour (i.e. to gain reward or find relief), which is in conflict with an awareness that the behaviour is not what one wants due to the problems it creates in one's life (Luigjes et al., 2019).

Compulsive behaviour is also highly prevalent within the general community, outside of DSM-5 defined mental illnesses (American Psychiatric Association., 2013), such as in compulsive eating and shopping (Figee et al., 2016; Tiego, Oostermeijer, et al., 2019a). Therefore, it is best conceptualised as existing on a continuum alongside normal behaviour, whereby normal controlled behavioural engagement sits at one end of the spectrum and severe, uncontrolled at the other. For example, everyone regularly eats, but fewer people regularly eat to the point of excess, despite not feeling hungry. This means there are likely differing degrees of compulsivity (i.e. ranging from low/mild to severe) which occur across a wide variety of behaviours (e.g. checking, cleaning, shopping, eating, gambling, alcohol use). Clinical populations, such as OCD or addiction, represent the more severe end of this spectrum. However, as this is an emerging area of research, the "tipping points" which demarcate the transition from benign to maladaptive compulsive behaviour are yet to be defined.

Investigating compulsivity across all levels of the continuum, from non-existent to severe, has the potential to identify early risk and perpetuating factors for compulsive behaviour, as well as the protective factors which may prevent problematic behaviour. It can also generate new insights and strategies to help individuals with sub-clinical compulsivity, who may be experiencing reduced quality of life but do not meet diagnostic

criteria. To date, research in this area has primarily focussed on individuals whose compulsive behaviours reach the threshold for diagnosis and have investigated discrete diagnoses separately (e.g. OCD, pathological gambling), meaning our understanding of basic risk and protective factors for transdiagnostic compulsive behaviour is largely based on narrow clusters of observable behaviours and the tail end of the continuum. In order to advance current treatments and develop preventative interventions, we need a more comprehensive picture of the full spectrum of compulsivity. For these reasons, the research investigations in the current thesis focus on transdiagnostic compulsive behaviour within non-clinical, community-based samples, in the hope of identifying characteristics associated with mild to moderate presentations of behaviour.

The following sections of this review will discuss compulsive behaviour within the context of the DSM-5 mental illnesses it is primarily associated (i.e. OCD, substance addiction and behavioural addictions). One only has to consider the pervasiveness of compulsivity across these illnesses and the associated personal and community level burden to understand the need to drive this field forward.

2.5. Disorders of compulsivity: burden of disease and clinical presentation

2.5.1. Obsessive-Compulsive Disorder

Burden of disease: OCD is probably the most well-known mental health disorder characterised by compulsivity. It is a chronically disabling condition with an estimated lifetime prevalence of 2-2.5% among the general population and it equally affects men, women and children of all races, ethnicities and socioeconomic backgrounds (Robins et al., 1984; Ruscio, Stein, Chiu, & Kessler, 2010). The course of OCD is typically lifelong and presents considerable burden to the individual and family, with severe impairment in function and quality of life (Koran, Thienemann, & Davenport, 1996). Disease burden is

further exacerbated by the high levels of comorbidities, with majority (57%) of OCD patients experiencing at least one other co-morbid diagnosis (Rasmussen & Eisen, 2002).

Treatment of obsessive-compulsive symptoms: When patients are newly diagnosed with OCD, the first treatments are typically either cognitive behavioural therapy (CBT), pharmacotherapy with serotonin reuptake inhibitors (SRIs) or a combination of both (Koran & Simpson, 2013). For those who do not respond to CBT and/or SRIs, alternative treatments include other types of psychotherapy, classes of medication other than SRIs, neuromodulation and in extreme cases, neurosurgery. It is estimated that only 20% of patients experience long-term remission of their symptoms following treatment, while 49% continue to experience clinically significant OCD (Bloch et al., 2013). Most adult patients with OCD do not experience symptom remission, emphasising the need for a better understanding of the underlying cause of disorder and the development of early-intervention preventative measures for at-risk (sub-subclinical) individuals.

Compulsivity in OCD: Obsessive-compulsive disorder is characterised by the presence of re-current and anxiety-provoking thoughts, images or impulses (obsessions), typically followed by repetitive ritualistic behaviours (compulsions) that are executed to relieve anxiety. The presentation of obsessions and compulsions can be remarkably heterogeneous and evolve over time, but predominantly fall into symptom dimensions of contamination obsessions and cleaning compulsions; harm concerns with checking-related compulsions; and obsessions regarding symmetry and the need for things to be “just right” paired with compulsions relating to ordering, arranging, and counting (Murphy, Timpano, Wheaton, Greenberg, & Miguel, 2010). These obsessions and compulsions cause significant distress, functional impairment and are very time-consuming.

It is generally agreed that the frequency of obsessions and compulsions, in addition to the degree that they interfere with functioning, is what distinguishes normal from

abnormal behaviour. Not all rituals or habits are compulsions, and while everyone will engage in these behaviours sometimes, a person with OCD will exhibit the following: (a) lack of control over thoughts and behaviours, even when they are recognised as excessive; (b) will spend at least one hour a day on these thoughts or behaviours; (c) doesn't get pleasure from performing the behaviour, but may feel relief from the anxiety the thoughts cause; and (d) experiences significant problems in their life due to these thoughts or behaviours (National Institute of Mental Health, 2016).

Subclinical obsessive-compulsive symptoms: Some individuals experience a milder, subclinical form of obsessions and compulsions. OCD symptoms are relatively common in non-clinical populations, with one epidemiological study estimating 22-26% of people experience obsession or compulsions and only 0.6% of these people meet the criteria for DSM diagnosis (Stein, Forde, Anderson, & Walker, 1997). Many of these people are designated as "subclinical OCD" because they share many of the same characteristics but do not meet the threshold for a clinical diagnosis. For example, subclinical individuals may endorse obsessions or compulsions and may engage in them for less than one hour a day or may not find them distressing. Subclinical symptoms can still cause social impairment, decreased life satisfaction and increased consultations to a doctor (Grabe et al., 2000), however, very few studies specifically investigating subclinical OCD have been conducted.

2.5.2. Substance addictions

Burden of disease: World-wide, one half of the adult population (2 billion people) use alcohol and 185 million adults are estimated to have used illicit drugs (Anderson, 2006). Many of these people will experience serious physical health, mental health, social and occupational consequences as a result of their use, with 3.3 million deaths occurring worldwide each year from the harmful use of alcohol and 200,000 from drug use (WHO, 2016). Of these individuals, 61 million will engage in binge drinking (men drinking $\geq$ 5

standard alcoholic drinks in one sitting; women $\geq$ 4 in one sitting), 17 million will develop an addiction to alcohol and 21.4 million an addiction to drugs (Mclellan, 2017).

Treatment of substance addictions: Despite the prevalence of addiction and the enormity of its consequences, only 1 in 10 people with an addiction will seek any form of treatment and less than half of those that do seek treatment will complete it (The National Center on Addiction and Substance Abuse, 2012). Treatments generally involve medications, 12-step groups, health care practitioners, and inpatient or outpatient rehabilitation (Grant et al., 2015). Often, these treatment programs bear little resemblance to the significant body of evidence-based practices that have been validated and are often inconsistent with scientific understanding (*Improving the Quality of Health Care for Mental and Substance-Use Conditions*, 2006). Moreover, substance addiction frequently co-occurs with other mental health conditions (Chan, Dennis, & Funk, 2008; Epstein, Barker, Vorburger, & Murtha, 2004) and multiple addictive behaviours are often involved (The National Center on Addiction and Substance Abuse, 2012). Despite this, conditions are often treated in artificial silos of care rather than holistically, meaning people need to seek treatment across multiple avenues (Mason, Wolf, O'Rinn, & Ene, 2017). High relapse rates and chronic trajectories are attributed to these ineffective treatment interventions (McLellan, Lewis, O'Brien, & Kleber, 2000).

Compulsivity in substance addiction Drug and alcohol addictions, referred hereafter as substance addictions, are characterised by (a) a repetitive drive to seek and consume the substance/s of choice, (b) loss of control in limiting intake, and (c) the emergence of negative emotional states (e.g. anxiety, irritability) when access to the substance is prevented (Koob & Le Moal, 2008). The desire to relieve the negative emotional states further drives the compulsion for the substance. Dual-process models of substance addiction (for review see McClure and Bickel, 2015) postulate that addiction is maintained

by an imbalance between “reflective” cognitive systems and “affective-automatic” systems. The automatic system is thought to be over-activated by emotional stimuli (i.e. consuming substance to relieve negative emotional state) and the reflective system is impaired, leading to an inability to adjust maladaptive behaviour despite long-term consequences. Key features of substance addiction are phenotypically similar to OCD. Firstly, in both cases there is an urge or ‘want’ to seek a substance or performing a behaviour. Secondly, there is a loss of control in ceasing use or behaviour. The use or behaviour is repetitively and inflexibly engaged in, despite causing functional impairment. Finally, negative emotional states often precede the use or behaviour, and are relieved to a degree following engagement.

Impulsive versus compulsive substance addiction: Impulsivity refers to a predisposition toward rapid, unplanned reactions with diminished regard to the negative consequences (Evenden, 1999). Similar to compulsivity, it characterises a number of clinical disorders and maladaptive behaviours involving repetitive actions, including substance addiction (Dick et al., 2010; Shin, Chung, & Jeon, 2013), pathological gambling (Loxton, Nguyen, Casey, & Dawe, 2008; Secades-Villa, Martínez-Loredo, Grande-Gosende, & Fernández-Hermida, 2016), overeating and food addiction (Loxton, 2018), pathological buying (Dell’Osso, Allen, Altamura, Buoli, & Hollander, 2008) and OCD (Abramovitch & McKay, 2016). In substance addiction, it is proposed that the shift from occasional but limited substance use to the emergence of a chronic dependent state represents a shift from impulsive to compulsive use (Koob, 2015; Koob & Le Moal, 2008; Koob & Volkow, 2010).

Impulsivity and compulsivity have traditionally been conceptualised as opposing ends of a spectrum, ranging from reward-seeking (i.e. impulsivity) to risk-avoidance (i.e. compulsivity; Hollander & Benzaquen, 1997). More recently however, they have been

conceptualised within a bi-directional model, as two underlying intermediate (i.e. transdiagnostic) phenotypes which overlap to produce a third general disinhibition phenotype (Chamberlain et al., 2019; Parkes et al., 2019; Tiego, Oostermeijer, et al., 2019). Although impulsivity and the bi-directional model are not the focus of the current thesis and will not be further discussed, they are important to acknowledge given the inter-relatedness with compulsivity, and the role of impulsivity in well-established models of substance addiction (Koob, 2015) and in growing models of behavioural addictions (Robbins & Clark, 2015) and OCD (Abramovitch & McKay, 2016).

2.5.3. Behavioural addictions

Alongside substance addictions, is another class of addictions that do not involve substances. Instead these are "behavioural" addictions, syndromes analogous to substance addiction where the frequently repeated maladaptive action is a behaviour, as opposed to consumption of psychoactive substances. These include the DMS-5 recognised gambling disorder (American Psychiatric Association, 2013), as well as other behaviours not yet included in the DSM, but receiving widespread research and public interest, including 'internet addiction', 'compulsive eating', 'gaming disorder' and 'compulsive shopping' (Robbins & Clark, 2015).

Burden of disease: It is difficult to estimate the collective burden of disease associated with each of these disorders, given the sheer number of behaviours that may fall under this umbrella. Gambling disorder alone affects 0.2-5.3% of adults worldwide and has an early age of onset, with a prevalence of 3-8% in adolescence and as many as 17% of youth gambling at least weekly (Petry, Stinson, & Grant, 2005). Compulsive eating, which encompasses a spectrum of eating behaviours ranging from passive overeating, binge-eating disorder and food addiction (Davis, 2013), also poses a significant threat to public health. Currently, over half the adult population is considered overweight or obese (World

Health Organisation, 2020), with researchers calling it a global "obesity pandemic" (Swinburn et al., 2011). Internet addiction has an estimated prevalence of 26.5% (Xin et al., 2018) and compulsive shopping a lifetime prevalence of 5.8% (Black, 2007). Behavioural addictions cause considerable burden of suffering to the affected individuals and their families and have a disorder trajectory which can be chronic and relapsing (Grant, Schreiber, & Odlaug, 2013).

Treatment of behavioural addictions: Gambling and binge-eating disorder will be used here to illustrate treatment approaches, as they are arguably the most widely studied behavioural addictions to date. Medication intervention is a common approach in substance addictions, however no medication has received regulatory approval for gambling disorder, and only one medication has received approval for the treatment of binge eating disorder (US Food and Drug Administration, 2015). Thus, there is a greater reliance on behavioural interventions for treatment. For gambling, this includes various combinations of CBT and motivational approaches, which tend to elicit moderate to high effect sizes and perform better than wait-list controls (Cowlishaw et al., 2012). However, the durability of such programs is unclear and high rates of relapse raise concerns over long-term treatment efficacy (Hodgins, Currie, El-Guebaly, & Diskin, 2007). In binge-eating disorder, CBT and interpersonal therapy are the most strongly supported interventions (Wilson, Wilfley, Agras, & Bryson, 2010). Although full recovery following treatment occurs in 64.4% and remission to sub-clinical in 80% of binge-eating patients, co-morbidities such as anxiety and substance use show tendencies towards relapse (Gregorowski, Seedat, & Jordaan, 2013; Hilbert et al., 2012), underscoring the need for transdiagnostic approaches to treatment.

Compulsivity in behavioural addictions: Like OCD and substance addictions, behavioural addictions are characterised by repetitive engagement in a certain behaviour; diminished control limiting a behaviour despite aversive consequences; and acute feelings

of reward or relief from negative emotions when the behaviour is engaged in (Chamberlain et al., 2016; el-Guebaly, Mudry, Zohar, Tavares, & Potenza, 2012). For example, in binge eating there is a loss of control limiting food intake, which is often preceded by negative emotions and/or rewarding beliefs about food (e.g. “eating makes me feel better”; Burton & Abbott, 2019). Feelings of guilt or shame also typically accompany binge-eating, which further exacerbates the desire to keep eating to seek temporary relief from negative emotions, despite ongoing health concerns. There are certain behaviours which are prone to excess and therefore at greater risk of being used compulsively (Punzi, 2016). Examples include behaviours such as shopping, eating, gambling, internet use. Although many individuals can engage in these behaviours without cause for concern, for a portion of the population there is risk these behaviours may become compulsive (Chamberlain et al., 2019).

To sum, compulsivity is a maladaptive behaviour that cuts across diagnostic boundaries and underlies several debilitating disorders, including OCD, substance addiction and behavioural addictions, as well as being prevalent at sub-clinical levels throughout the community. All are characterised by early onsets, chronic trajectories and poor treatment outcomes, highlighting the need to develop new understandings of underlying aetiology of disorders to inform more efficacious preventative and treatment approaches. Similar outcomes and reduced quality of life also accompanies subclinical compulsivity, emphasizing the importance of investigating the full severity spectrum of compulsive behaviours. Although many researchers now recognise the need to investigate compulsive behaviours from a transdiagnostic perspective, our understanding of the underlying predisposing and perpetuating factors remains largely incomplete.

CHAPTER THREE

3. Psychological, cognitive and neurobiological drivers of transdiagnostic compulsive behaviour

Investigations into the underlying causes of compulsivity have found it to be a highly complex and multifaceted construct (Fineberg et al., 2018). There is not one singular factor that leads to compulsive behaviour, but rather multitudes of factors (e.g. psychological, cognitive, neurobiological factors), in various combinations, that constitute greater risk or likelihood of compulsivity (Figee et al., 2015). As will be shown in this chapter, the evidence to date has largely focused on cortico-striatal-thalamic-cortical (CSTC) models for understanding compulsivity. That is, compulsivity as a product of disrupted CSTC neurocircuitry and the cognitive and psychological processes these circuits engender. These include cognitive processes such as habit learning, cognitive flexibility and reward processing, as well as psychological processes including motivations for reward and intolerance of uncertainty. When viewed as a whole, this existing body of CSTC work reveals that categorically distinct compulsive behaviours, such as OCD and addictions, can stem from the same underlying process disruptions, thus supporting a transdiagnostic conceptualisation of compulsive behaviour (Harrison et al., 2013; Jung et al., 2017; Parkes et al., 2019).

However, as this is relatively new area of research, it remains limited in certain ways. Firstly, current understanding is mainly based on comparing findings from investigations into discrete behaviours (e.g. OCD versus addiction), with very few studies utilising transdiagnostic samples. Transdiagnostic samples (i.e. samples that are focussed on more than one DSM or ICD diagnostic population) are needed to characterise the heterogeneity and overlap of symptoms across diagnostic categories. Secondly, the full spectrum of processes that predispose and perpetuate compulsivity is not well understood. Although

there is good support for CSTC systems, few studies have explored alternate models. Specifically, the role of affect-driven processes and limbic neurocircuitry in compulsive behaviour has been largely overlooked and may be important to consider due to its potential strength in explaining symptom presentation.

In the current chapter, I will provide an overview of the psychological, cognitive and neurocircuitry evidence demonstrating that compulsive behaviour may stem from disruptions to CSTC circuits and processes related to CSTC function. Although a comprehensive body of literature exists, in the present chapter I will focus on the most central findings to highlight that different compulsive behaviours have common underlying causes. Where possible, the discussion will focus on studies using transdiagnostic samples. After establishing this evidence base, preliminary support for the role of affective systems will then be discussed, highlighting it as a relatively under investigated area in compulsivity literature and warranting further investigation.

3.1. Cortico-striatal-thalamic-cortical dysfunction in compulsive behaviour

The cortico-striatal-thalamic-cortical circuits play a critical role in compulsive behaviour (Harrison et al., 2013; Jung et al., 2017; Parkes et al., 2019) and have historically been implicated in a range of behavioural control functions involving motor, cognitive and motivational processes (Cummings, 1993). These circuits involve direct and indirect pathways projecting from areas of the cortex to subcortical regions, such as the striatum and thalamus, and back to the cortex. The striatum refers to a small group of sub-cortical structures including the putamen, caudate nucleus and nucleus accumbens (NAC).

Changes in the net excitation or inhibition of cortical and sub-cortical regions contributes to the initiation/continuation and inhibition/switching of behaviours (Jahanshahi & Rothwell, 2017). Healthy human behaviour requires flexibility between the initiation and inhibition of behaviours and disruptions to these circuits can result in

difficulties ceasing maladaptive and habitual behaviours. To illustrate, healthy behaviour would be discontinuation of a behaviour once it has served its initial intended purpose (e.g. checking the door is locked once) or recognising when it is causing functional impairment and stopping (e.g. not placing another gambling bet because substantial money has already been lost). As will be discussed, disruptions to CSTC circuits can impair the ability cease automatic habitual behaviours, respond flexibility and control reward-seeking drives, thus making it difficult to maintain healthy human behaviours

3.1.1. Increased habit learning and reduced goal-directed control in compulsive behaviour

Habits are defined as inflexible, cue-elicited, automatic behaviours performed without consideration of consequences (Balleine & Dickinson, 1998; Gillan & Robbins, 2014; Ostlund & Balleine, 2008; Vandaele & Janak, 2017). They are considered the opposite of goal-directed behaviours which are intentional, thoughtful and sensitive to the value of prospective goals. It has been proposed that compulsive behaviours can be conceptualised as excessive habits which develop at the expense of goal-directed behaviour (Gillan, Robbins, Sahakian, van den Heuvel, & van Wingen, 2015). Stronger formation of habits has been demonstrated across diverse compulsive disorders. For instance, one study compared responses on a reward probability decision-making task in a transdiagnostic sample of individuals with binge eating, methamphetamine addiction and OCD, and found a significant bias towards more habit-like responding (i.e. responses based on previously rewarding stimuli rather than outcome predictions using updated probability information) across all the disorders (Voon et al., 2015). Investigations using non-transdiagnostic samples also reveal a strong bias toward habit formation is evident in the different disorders. In comparison to controls, patients with OCD are more prone to “slips of action” and less goal-directed actions on tasks designed to assess behavioural control (Gillan et al., 2011; Gillan & Robbins, 2014), suggesting an increased reliance on habitual responding. Patients with

alcohol dependence also show imbalances toward habit learning over goal-directed action (Sjoerds et al., 2013). Therefore, a cognitive bias towards forming habits may constitute a vulnerability or exacerbating factor for compulsive behaviour, as the individual has less control over automatic and inflexible responses.

Imbalances in habitual over goal-directed control of behaviour can be mapped onto underlying abnormalities in CSTC connectivity. A recent study investigated the relationship between CSTC effective connectivity and the severity of transdiagnostic compulsive behaviour (Parkes et al., 2019). In a population of individuals with OCD and gambling disorder, researchers showed that CSTC effective connectivity did not differ as a function of diagnostic labels but did differ based on symptom severity and compulsivity. Specifically, higher symptom severity and compulsivity on self-report measures were associated with reduced bottom-up connectivity in the dorsal CSTC circuit, as compared to healthy controls. Dorsal CSTC dysfunction contributes to deficits in the goal-directed control over behaviour (Gillan et al., 2015), suggesting it may drive the continuation of compulsive behaviour despite it conflicting with long-term goals.

3.1.2. Reduced cognitive flexibility in compulsive behaviour

Cognitive flexibility is broadly defined as the ability to dynamically adjust behaviour to the demands of a changing environment (Dajani & Uddin, 2015). Compulsive behaviours are characterised by a diminished ability to stop or divert unwanted ideas or actions, suggesting the presence of cognitive inflexibility. Comparing individuals with alcohol dependence, pathological video-gaming, binge eating disorder, compulsive sexual behaviour and healthy controls, Banca, Harrison and Voon (2016) found evidence of cognitive inflexibility across all the different pathologies in the form of impaired reversal learning, attentional set-shifting difficulties and perseveration. Similar cognitive profiles have been observed in other transdiagnostic studies of alcohol dependence and pathological gambling

(Vanes et al., 2014), as well as within OCD, pathological video-gaming and alcohol use disorder (Kim et al., 2017). Investigations into individual diagnostic categories further support cognitive inflexibility as a core feature in OCD (Menzies et al., 2007), substance use (Izquierdo & Jentsch, 2012) and behavioural addictions (Vanes et al., 2014). Although this finding may not be universal across compulsive behaviours, with no impairments found in compulsive buying disorder (Derbyshire, Chamberlain, Odlaug, Schreiber, & Grant, 2014).

During reversal-learning tasks, which require high cognitive flexibility, individuals with OCD demonstrate defective recruitment of the OFC (a region within the CSTC system; Chamberlain et al., 2008; Freyer et al., 2011), as do individuals with substance use problems (Izquierdo & Jentsch, 2012). In a study investigating both OCD and substance dependence, it was found that compulsive symptom severity directly correlated with reduced OFC connectivity in both pathologies (Meunier et al., 2012). Taken together, disruptions in CSTC appear to underlie difficulties with cognitive flexibility, which in turn impacts the ability to alter behaviour when it becomes maladaptive or inappropriate to the functional context. This may explain why compulsive individuals continue to rigidly engage in certain behaviours despite consequences. For example, frequently using alcohol to relieve feelings of stress, when other more adaptive behaviours (e.g. exercise, relaxation techniques, confiding in a friend) would be more appropriate and helpful.

A psychological process related to cognitive inflexibility is intolerance of uncertainty, which is defined as a general inability to cope with unpredictability of ambiguity. Individuals with high intolerance of uncertainty have a lower threshold for doubt. In situations that others would accept to be sufficiently certain, people with high intolerance of uncertainty may perceive the situation as unclear (Ladouceur, Talbot, & Dugas, 1997) and are more likely to interpret ambiguous information as threatening (i.e. uncertainty = danger; Reuman, Jacoby, Fabricant, Herring, & Abramowitz, 2015). Although uncertainty itself can be

adaptive (e.g. double checking your work to make sure there are no mistakes), this construct is differentiated by being a disproportionately a negative reaction to unpredictable events that are inevitably a part of everyday life. Thus, intolerance of uncertainty can be conceptualised as a form of inflexibility or rigidity (Fergus & Rowatt, 2014).

In relation to compulsivity, individuals with OCD often describe how their obsessions trigger doubt about something, and how their compulsions function to relieve such doubt and restore 'certainty' (Abramowitz, Taylor, & McKay, 2009). There is a consistent, positive relationship between self-reported intolerance of uncertainty and OCD symptoms (Holaway, Heimberg, & Coles, 2006; Tolin, Abramowitz, Brigidi, & Foa, 2003). Self-reported intolerance of uncertainty is also significantly higher in people with binge eating disorders (Bartholdy et al., 2017), is associated with increased drive to use alcohol (Oglesby, Albanese, Chavarria, & Schmidt, 2015) and is related to increase use of drugs to cope (Doruk et al., 2015). Moreover, intolerance of uncertainty has been linked to CSTC dysfunction and greater symptom severity in a transdiagnostic compulsive populations (Parkes et al., 2019), supporting it as a likely risk and/or maintenance factor for compulsive behaviour. Overall, a consistent line of evidence has emerged across multiple levels of function (i.e. psychological, cognitive and neurocircuitry) indicating that inflexibility and intolerance are key processes which contribute to compulsivity.

3.1.3. Altered reward processing in compulsive behaviour

Finally, dysfunction within CSTC circuits involved in reward processing have been heavily implicated in both OCD and addiction, whereby there is a tendency to accept smaller more immediate rewards over larger delayed ones or long-term goals. In a recent meta-analysis of 25 studies investigating reward processing, decreased striatal activation during reward anticipation in monetary reward tasks was a consistent finding in substance-use and

gambling addictions when compared to healthy controls (Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017). This demonstrates a reduced brain activity response to non-addiction related cues and is typically mirrored by an increased response to addiction cues (Robinson & Berridge, 2008). Similarly, in OCD attenuated reward anticipation activity is evident in the ventral striatum when compared to controls (Figee et al., 2011) and is accompanied by increased striatal responsiveness in response to symptom-specific stimuli (Rotge et al., 2008). Therefore, in compulsivity the striatum may become conditioned to respond to a certain stimulus (e.g. alcohol, gambling, cleanliness etc.), releasing an acute reward/pleasure response and promoting increased salience and further engagement with that stimulus.

Beyond such neuroanatomical evidence, abnormalities in reward processing are also observed at the psychological level, whereby compulsive individuals self-report greater sensitivity to reward or a stronger drive to seek reward. Impulsivity, a psychological trait strongly associated with motivations for reward (Corr, DeYoung, & McNaughton, 2013) and linked to CSTC function (Fineberg et al., 2014), is observed across substance and behavioural addictions, irrespective of the type of addiction (Zilberman et al., 2018). This supports the idea that different compulsive behaviours may stem from common psychological processes linked to reward motivation. These findings converge with another study examining personality traits in substance use disorder, gambling disorder and bulimia nervosa, which found novelty seeking (i.e. a sub-facet of impulsivity and defined as a pursuit of rewarding new experiences) to be elevated across all behaviours (del Pino-Gutiérrez et al., 2017).

Although OCD has traditionally been conceptualised as being motivated by avoidance of negative internal experiences, recent evidence shows that for some patients with OCD compulsions may be rewarding, rather than relieving. Studies of treatment seeking OCD patients have revealed most patients experience positive affect (e.g. feeling

cheerful, proud, determine, confident, energetic and alert) in anticipation of and following their compulsion (Fontenelle et al., 2015; Ferreira, Yücel, Dawson, Lorenzetti, & Fontenelle, 2017).

The evidence above collectively suggests there are individuals with OCD and addiction for whom perpetuation of their compulsive behaviours includes reward motivations. Notably, self-reported impulsivity, coupled with intolerance of uncertainty, has been found to better account for CSTC disruptions in comparison to traditional diagnostic categories of OCD and gambling disorder (Parkes et al., 2019), indicating their superiority in explaining brain-behaviour relationships and illustrating how integration of multiple measures (as opposed to a single measure) can be a more sensitive method for capturing neurobiological variance.

Overall, there is good emerging evidence for CSTC models in explaining compulsivity. Evidence has been found across multiple levels of function, further supporting it as a good framework for understanding compulsivity. As has been shown, abnormalities in reward processing, cognitive flexibility and habit learning likely predispose one to, or exacerbate, compulsive behaviours. Disruptions across multiple processes (e.g. reward processing + habit learning; intolerance of uncertainty + impulsivity) likely contribute additive vulnerability. However, these processes do not entirely explain compulsive behaviour and further research is necessary to uncover other models of understanding, and thus other processes which contribute to compulsivity.

3.2. Affective processing and limbic dysfunction in compulsive behaviour

In comparison to CSTC models of compulsivity, our understanding of the cognitive and neural substrates that underlie affect-driven compulsive behaviour is relatively underdeveloped, particularly in relation to the role of negative affective states. Despite evidence from discrete diagnostic samples indicating that limbic systems may be disrupted

in disorders of compulsivity, research is yet to explore affective models and limbic neural systems as a way to understand transdiagnostic compulsive behaviour.

In substance addictions, drug-use shifts from reward driven, to avoidance of negative emotional states. This is mirrored by recruitment of the brains anti-reward systems, of which the amygdala is an important region (for review see Koob, 2015). There is also a reduction in top-down prefrontal control over the amygdala, allowing it to be more active and generate emotion (Crunelle et al., 2015). Excessive amygdala and insula activation have been linked to increased severity of craving toward gambling stimuli in people with this condition (Goudriaan, De Ruiter, Van Den Brink, Oosterlaan, & Veltman, 2010). Similar findings are also seen in binge eating, whereby there is greater activation in bottom-up emotion generating regions in response to food cues, and reduced top-down control from higher order networks (Steward, Menchon, Jiménez-Murcia, Soriano-Mas, & Fernandez-Aranda, 2018). This could explain why people compulsively eat food, experiencing increased emotional salience towards food in the context of reduced self-regulation, while other people are able to inhibit this behaviour and monitor their intake using executive control. Taken together, regions within the limbic system appear to be over-activated and this is coupled with less control from high-order cortical regions, suggesting there may be an affective drive underlying compulsivity in addiction.

Beyond these substance addiction presentations, there is also ample evidence suggesting dysfunction within affect regulatory neurocircuits contribute to symptom presentation in OCD (summarised in a review by van den Heuvel et al., 2015). Specifically, there is a disconnection between limbic regions and top-down fronto-parietal regions (Göttlich et al., 2014), which is thought to explain why individuals with OCD struggle to re-appraise and regulate their emotions (de Wit et al., 2015), and thus rigidly rely on overt

behaviours (e.g. cleaning, checking, arranging) to down-regulate uncomfortable emotions (e.g. anxiety, worry).

Overall, there is strong emerging evidence to suggest there are abnormalities in brain structure and function which are common across a range of disorders characterised by compulsivity. However, this area of research is still underdeveloped, and the full range of both psychological and cognitive risk factors remains poorly understood. This is particularly the case for affect-driven compulsive behaviour, which offers an exciting new opportunity to progress understanding of compulsivity and its causes. In the subsequent chapters I will expand upon this foundation of research, by exploring the model of Experiential Avoidance, which provides a promising framework for understanding affect-driven compulsive behaviour.

CHAPTER FOUR

4. Experiential avoidance: A psychological driver for compulsive behaviour

Compulsive behaviour can be viewed as a maladaptive way to manage ones emotions (Figee et al., 2016). Behaviours which are vulnerable to excess (e.g. checking, alcohol-use, gambling, shopping, eating) provide effective strategies to alter or avoid negative emotions. For example, in OCD repetitive behaviours (e.g. checking, washing, ordering) are often engaged in to reduce anxiety or distress. In substance addiction, consuming substances immediately alters the internal emotional experience, offering a short-term method of escape or relief. In behavioural addictions, behaviours such as gambling or excessive internet use can provide useful means of distraction from internal thoughts or worries. This occurrence, when individuals are unwilling to tolerate uncomfortable thoughts or emotions and take-action to avoid them, is known as Experiential Avoidance (EA; Hayes et al., 2004). Despite being a potentially potent motivator of compulsive behaviour, EA has received relatively little attention in compulsivity literature and has not yet been investigated transdiagnostically. In this chapter I will outline the background theory of EA, provide rationale for its relevance in transdiagnostic compulsive behaviour and present the available evidence from the literature to date. This information is used to inform the affective processes discussed in the subsequent chapter (Chapter 5) and is the framework of understanding which Studies One and Two (Chapter 6 and 7) are based upon.

4.1. Background theory of experiential avoidance

EA is comprised of two related parts: (a) an unwillingness to remain in contact with negative private experience (e.g. memories, thoughts, emotions), and (b) action taken to alter or avoid these private experiences (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996).

In other words, EA is a core psychological construct that arises when people have uncomfortable or unwanted thoughts and/or emotions and act in order to avoid them. It can be thought of as an individual's relationship with distress versus his or her actual perceived distress, how someone responds to feelings, rather than what he or she is feeling.

As humans, is it natural to wish to avoid negative experiences, however such experiences are often necessary to achieve our goals. For example, emotions such as stress and self-doubt are unpleasant, however they are emotions which must be experienced in many of life's circumstances, such as job interviews, meeting new people, raising children etc. They are a necessary component of living a valued life. Individuals who are experientially avoidant have a lower threshold for negative emotions and more readily seek relief or avoidance from them. In the short-term, avoidance is often effective, as it immediately works to reduce or alleviate negative feelings or distress. However, EA becomes a disordered process when it is applied rigidly and inflexibly, such that enormous time, effort and energy is devoted to managing, controlling or struggling with unwanted emotions (Boulanger, Hayes, & Pistorello, 2010). This creates long-term difficulties (i.e. psychopathology) as certain emotions are negatively evaluated and avoided, like actual external threats. EA exacerbates the level of psychological distress by increasing the salience of negative emotions – i.e. greater effort used to avoid negative emotions, results in increased monitoring for the presence of these emotions (Pickett & Kurby, 2010). Therefore, while it is an adaptive strategy at reducing short-term distress, it is maladaptive long-term as it paradoxically works to increase overall distress.

4.2. Measurement of experiential avoidance

Before discussing the empirical evidence for EA in mental health, it is important to understand how it is measured, as this impacts interpretation of empirical evidence. The measurement of EA is complicated, as it encompasses a wide variety of behaviours. For

example, cognitive avoidance strategies such as thought suppression (Wenzlaff & Wegner, 2000), affective strategies such as emotional suppression (Gross & Levenson, 1993) and behavioural methods of avoidance coping (Zeidner & Endler, 1996), can all be conceptualised as types of EA (Hayes et al., 2004).

Researchers have developed self-report scales to simplify and capture EA as one unified construct. The psychometric scale most widely used is the Acceptance and Action Questionnaire (AAQ-II), which was developed by Hayes et al. (2004) and has since been updated from the AAQ-I. It is a short scale specifically designed to measure EA, with questions such as "*I worry about not being able to control my worries and feelings*". Research using the AAQ has linked EA with a wide variety of psychopathology (for review see Chawla & Ostafin, 2007) and while these results are promising, it should be noted that this measure of EA is limited in certain ways. Firstly, some studies have shown that the AAQ has poor content validity and actually functions more as a measure of neuroticism and negative affect (Boelen & Reijntjes, 2008; Rochefort, Baldwin, & Chmielewski, 2018). Secondly, the AAQ is a brief measure which was designed to assess two aspects of EA (i.e. *non-acceptance* and *avoidance* of negative internal experiences), which is problematic given the broad scope and complexity of EA as a construct. The final and most notable limitation of the AAQ, is that it treats EA as a unidimensional construct.

In an empirical review of EA, Chawla and Ostafin (2007) concluded that EA is best conceptualised as a multidimensional construct encompassing a number of different processes. The multidimensional nature of EA has been supported in more recent empirical studies (Gámez, Chmielewski, Kotov, Ruggero, & Watson, 2011; Mcmullen, Taylor, & Hunter, 2015; Rochefort et al., 2018). In response to the review by Chawla and Ostafin (2007), the Multidimensional Experiential Avoidance Questionnaire (MEAQ) was developed to capture EA across six dimensions: behavioural avoidance, distress aversion, distraction

and suppression, repression/denial, procrastination, and distress endurance (Gámez et al., 2011). Unlike the AAQ, the MEAQ can be differentiated from neuroticism/negative affect and is accepted as the most valid available measure of EA (Rochefort et al., 2018).

Alongside challenges associated with measuring EA, there is also variability around whether EA should be conceptualised as trait-based or state-based. Research generally conceptualizes EA as an avoidance strategy (i.e. state-based) and therefore typically investigates it as a mediator variable, occurring further downstream and influencing how other trait-based variables related to psychological outcomes (Fledderus, Bohlmeijer, & Pieterse, 2010; Ghazanfari, Rezaei, & Rezaei, 2018; Kashdan, Barrios, Forsyth, & Steger, 2006; Kingston, Clarke, & Remington, 2010; Orcutt, Pickett, & Pope, 2005; Roche, Kroska, Miller, Kroska, & O'Hara, 2018). EA has also been investigated as a moderator, whereby it explains the conditions under which other psychological constructs predict behaviour (Bardeen, Fergus, & Orcutt, 2013; Minami, Bloom, Reed, Hayes, & Brown, 2015; Pickett, Bardeen, & Orcutt, 2011). Most recently however, EA has been conceptualised as a trait-like characteristic (Kirk, Meyer, Whisman, Deacon, & Arch, 2019), characterised by an unwillingness to tolerate negative emotions which in turn influences avoidant behaviour in the context of distress. This perspective is reflected in newer measures of EA (i.e. MEAQ), which now assess it as a trait (Gámez et al., 2013, 2011).

4.3. Evidence for experiential avoidance in mental health disorders

EA has received increasing attention in the clinical psychology literature due to growing interest in "third-wave" behavioural and cognitive therapies, of which EA is a central theme (Boulanger et al., 2010). Examples of third-wave therapies include acceptance and commitment therapy (ACT), mindfulness-based cognitive therapy (MBCT), behavioural activation and dialectical behaviour therapy (DBT). These therapies target pathological experiential avoidance processes and seek to foster experiential acceptance of internal

experiences. Multiple meta-analyses have supported the efficacy of these therapies and the constructs they target, indicating they are generally as effective as traditional cognitive behaviour therapy (CBT; Dimidjian et al., 2016; Hacker, Stone, & MacBeth, 2016; Öst, 2008).

Evidence demonstrates that EA is a key process which contributes to the development and maintenance of various forms of psychopathology (Chawla & Ostafin, 2007; Monestès et al., 2016). In a meta-analysis of 32 studies involving 6,628 participants investigating the relationship between EA (as measured by the AAQ) and various measures of psychological wellbeing, quality of life and psychopathology, it was found that EA accounted for 16-28% of the variance in mental health outcomes, including depression, anxiety and lower quality of life (Hayes et al., 2004). While this work has largely used the AAQ, promising findings have also emerged from research using the MEAQ. Using this measure, EA has been linked to reduced wellbeing (Machell, Goodman, & Kashdan, 2015), depression (Moroz & Dunkley, 2019), eating problems (Ciarrochi, Sahdra, Marshall, Parker, & Horwath, 2014; Litwin, Goldbacher, Cardaciotto, & Gambrel, 2017) and substance use (Buckner & Zvolensky, 2014; Buckner, Zvolensky, Farris, & Hogan, 2014; Dvorak, Arens, Kuvaas, Williams, & Kilwein, 2013). Despite its role across a wide range of pathologies, EA has rarely been used to investigate psychopathology transdiagnostically.

4.4. Experiential avoidance in compulsive behaviour

4.4.1. Experiential avoidance in obsessive-compulsive behaviours

EA is believed to play an important role in OCD and it has been posited that compulsions can be conceptualised as forms of EA (Eifert & Forsyth, 2005; Hayes et al., 1996). Obsessions are persistent thoughts/impulses/images that are associated with significant anxiety and distress. Compulsions are repetitive behaviours (e.g. checking, cleaning) or mental acts (e.g. counting) which are inflexibly and excessively engaged in to

relieve anxiety provoked by obsessions. The goal of the compulsion is to reduce and control the obsession and associated anxiety. Analogous to EA, the compulsion is being used to relieve uncomfortable thoughts and/or emotions.

Despite the good theoretical rational for the role of EA in OCD, only a handful of studies have directly investigated the relationship and findings have been mixed. Two studies explored the ability of EA to predict obsessive-compulsive symptoms in a non-clinical sample and found that it did not add significantly to the prediction of symptoms, over and above the contribution of general distress and obsessive beliefs (Abramowitz, Lackey, & Wheaton, 2009; Manos et al., 2010). Another study however, using more sensitive measures of EA (i.e. the AAQ-II rather than the AAQ-I), found that EA was significantly, positively correlated with self-reported OC symptom severity (Wetterneck, Steinberg, & Hart, 2014), albeit the relationship was weak (r = .42). The role of EA has not yet been investigated in OCD using more recently developed sensitive and multidimensional measures. It therefore remains unclear whether mixed findings from past literature are due to problems with EA conceptualisation and measurement validity. Moreover, it may be that certain lower order constructs of EA (e.g. behavioural avoidance) and more important for our understanding of OC behaviour and assessing EA as a unitary construct reduces specificity to detect these effects.

4.4.2. Experiential avoidance in substance-related addictions

Similarly, relatively few studies have directly examined the role of EA in substance addictions, despite the similarities in addiction phenomenology and EA. Positive reinforcement dominates the early stages of substance use, whereby expectation of reward motivates use (Koob & Volkow, 2010). However, in the later stages, there is a transition from positive reinforcement to negative reinforcement and automaticity, where avoidance of negative affect motivates use. These later stages encourage more compulsive use of

substances and are the stages most analogous to EA. Here, the individual is experiencing an uncomfortable thought/feeling/emotion (e.g. withdrawal/negative affect) and seeks short-term immediate relief with further substance consumption. Moreover, this occurs despite awareness that further consumption causes functional impairment. Interestingly, while the typical conceptualisation of addiction is the transition from positive to negative reinforcement, for some individuals early substance use is motivated by negative reinforcement (Conrod, 2016). Meaning, the initial purpose of use was to seek relief/avoidance from negative internal emotions or experiences, and further supporting the relevance of EA for understanding addictions.

Research directly investigating EA and addiction is sparse, however there is literature to support that substances are used to alter negative internal experiences. For example, alcohol misuse is a commonly reported strategy for coping with negative affect (Ehrenberg, Armeli, Howland, & Tennen, 2016), disengaging from social stressors (Blumenthal, Ham, Cloutier, Bacon, & Douglas, 2016) and avoiding emotional arousal (Brotchie, Hanes, Wendon, & Waller, 2007). Similarly, people who have experienced significant life stressors often turn to substances such as alcohol (Bedard-Gilligan, Cronce, Lehavot, Blayney, & Kaysen, 2013), cocaine (Back, Sonne, Killeen, Dansky, & Brady, 2003), marijuana (Bonn-Miller, Vujanovic, Feldner, Bernstein, & Zvolensky, 2007) or opiates (Rugani et al., 2011) to repress psychological distress.

The small number of studies that have used direct measures of EA have elicited promising findings. Using the multidimensional measure of EA, Buckner, Zvolensky, Farris, & Hogan (2014) showed that among current cannabis users, procrastination (i.e. delaying anticipated distress), behavioural avoidance (i.e. overt avoidance of distressing situations) and denial (i.e. dissociating from distress) were all associated with a greater frequency of cannabis-related problems. In particular, behavioural avoidance was *predictive* of cannabis-

related problems, leading authors to conclude that those who use cannabis as a behavioural strategy to cope with distressing situations are more likely to display problematic drug-related behaviour. Another study compared problematic alcohol use in college students with a history of trauma (Dvorak et al., 2013). Higher PTSD symptomology coupled with low distress endurance (i.e. ability to behave effectively when under distress) predicted greater comorbid alcohol related consequences, indicating that greater distress endurance is protective for comorbid substance related problems. Taken together, EA appears to play a role in substance-related addiction, however this is difficult to conclude given the relatively few studies directly assessing the relationship.

4.4.3. Experiential avoidance in behaviour-related addictions

Individuals with gambling problems use gambling to regulate a range of unwanted private experiences (Fong, 2005; Wood & Griffiths, 2007). However, only one study has directly investigated this within the context of EA. In treatment seeking problem gamblers, EA was found to be predictive of higher levels of problem gambling (Riley, 2014). Moreover, EA mediated the positive association between thought suppression (i.e. individual's tendency to suppress unwanted negative thoughts) and problem gambling. Meaning, EA was not only related to problem gambling, but believed to be a mechanism through which unhelpful psychological strategies operated.

Compulsive buying involves a preoccupation with buying or impulses to buy that are experienced as irresistible, intrusive, and uncontrollable (McElroy, Keck Jr, Pope Jr, Smith, & Strakowski, 1994). EA has been found to partially mediate the relationship between distress tolerance (i.e. perceived ability to withstand distress) and compulsive buying (Williams, 2012). This indicated buying behaviours, when they occur in the context of distress or negative mood, may serve an avoidant, or negatively reinforcing function.

EA has also been implicated in compulsive eating. Compulsive eating includes problematic behaviours such as 'emotional' eating or binge eating. Emotional eating is defined as the tendency to eat in response to negative emotions (Arnow, Kenardy, & Agras, 1995). Binge eating is similar, however has specifiers related to time frame (i.e. food consumed within a 2-hour period), amount of food consumed (i.e. large) and feeling a loss of control (American Psychiatric Association, 2013). Both behaviours are characterised by individuals who eat in response to cues that signal psychological distress as opposed to physiological cues that signal hunger (Allison, Grilo, Masheb, & Stunkard, 2005; Greeno & Wing, 1994; Oliver, Wardle, & Gibson, 2000). EA is thought to mediates this relationship between negative emotions and emotional eating (Litwin et al., 2017). Furthermore, in a study evaluating the efficacy of ACT for binge eating, results showed that improved treatment outcomes were mediated by reductions in EA (Lillis, Hayes, & Levin, 2011).

Overall, there is good theoretical and emerging empirical evidence in support of a relationship between EA and compulsive behaviour across a range of individual diagnoses and behaviours. However, this body of work is clouded by conceptual and statistical variability in the measurement and assessment of EA. Moreover, no research studies have explored this relationship transdiagnostically, across multiple compulsive behaviours within the one integrated research protocol. Delineating the nature of this relationship will help to inform more targeted and individualized interventions for compulsivity.

CHAPTER FIVE

5. Compulsive behaviour and associations with cognitive and neurobiological affective processing

In the RDoC initiative, emphasis is placed on understanding the fundamental mechanisms that result in differing degrees of dysfunction, in terms of basic science (e.g. neurocircuitry, physiology, cognition). In keeping with this approach, I will now focus on several basic brain mechanisms that have demonstrated good theoretical and experimental evidence to suggest that they contribute to or exacerbate experientially avoidant compulsive behaviour. These include cognitive valence learning asymmetry (i.e. a bias in learning and forming expectations based on positive versus negative feedback, as measured by a computer-based task), Hypothalamic-Pituitary-Adrenal (HPA) axis activity (as measured by the cortisol awakening response) and amygdala network activity (as measured by resting-state functional connectivity). The mechanisms selected are related to 'hot' cognitive processes as opposed to 'cool' processes (Zelazo & Carlson, 2012). Cool cognitive processes are those that operate in affectively neutral contexts and generally require logic and conscious control, for example cognitive flexibility, planning and working memory. In contrast, hot cognitive processes are those elicited in contexts that generate emotion, motivation and conflict between acute gratification and long-term goals, for example delay gratification and affective decision making. Given the role of emotion in experientially avoidant compulsive behaviour, it seemed pertinent to select processes with a known role in emotionally driven behaviour. The aforementioned mechanisms inform the outcome measures of the Study Two, thus a detailed discussion of the background theory and measurement of each will be provided. This will be followed by insights into how these processes may directly relate to EA and compulsivity.

5.1. Valence learning asymmetries

5.1.1. Theory of valence asymmetries

In our day-to-day life, we are often faced with decisions to approach or avoid the situations we encounter. Some decisions are automatic and easy, while others require more thoughtful consideration. These daily decisions can have consequences that impact various aspects of our health, happiness and life. For example, deciding whether to exercise today. The effort required for each decision is influenced by how motivated we are to approach/avoid a situation, as well as our expectations of that situation. For example, we may feel motivated to get fitter, however our expectation of exercise is negative (e.g. painful and tiring). This would make for a more effortful deliberation over whether to exercise, in comparison to someone who was feeling motivation and had positive expectations about exercise (e.g. feeling healthy and energised).

The literature on cognitive valences asymmetries is born out of work by Fazio and colleagues (2015), who proposed there are individual differences in the tendency to weight positive versus negative information when forming *expectations* about situations, as well as *learning* positive or negative associations about a situation. It is further posited that individual differences in valence weighting reflect differences in how pre-established attitudes generalise onto similar but novel situations. For instance, individuals with a negatively weighted bias notice resemblance to known negatives more strongly than negatives to known positives and are therefore more likely to make a negative assessment of the novel situation. For example, someone with a negatively weighted bias may make a negative initial assessment of a new form of exercise (e.g. Zumba) because of its resemblance to the negative aspects of other forms of exercise (e.g. “I have ran before and it was painful, this will be painful as well”). This may be analogous to people who tend to see the negatives in new situations, versus people who tend to see the positives.

Importantly, our valence asymmetries influence our behaviour. Given a positive expectation of a situation, one is more likely to approach and engage. Conversely, a tendency to generalise negative expectations may lead to avoidance like behaviours. Take the exercise example again; the individual with the positive valence asymmetry may weigh the positives associated with exercise (i.e. feeling energised, feeling fit) more strongly than the negatives (i.e. discomfort, fatigue, effort), and therefore be more likely to regularly exercise and explore new types of exercise. While for someone who generalises more negative expectations, the discomfort/fatigue/effort associated with exercise will outweigh and be more salient than the positives, thus leading to a reduced likelihood of engaging in exercise and exploring new forms of exercise.

5.1.2. Measurement of valence asymmetries: BeanFest

To assess individual differences in valence asymmetries, Fazio and colleagues (2015) developed a highly novel cognitive task called BeanFest. BeanFest comprises two stages, a leaning phase which establishes the players tendency to learn and remember from situations that resulted in punishment versus reward, followed by a generalisation phase during which their unconscious propensity to generalise this bias to novel situations or events is examined. During the learning phase, participants attempt to maximise their points by learning to approach positive (i.e. rewarding) and avoid negative (i.e. punishing) stimuli. The stimuli are "beans" which vary in appearance (*Figure 5.1*). Following this learning phase, they are then asked to classify the beans as either "helpful" or "harmful". These beans in the classification phase include beans from the learning phase, to assess learning, and novel/new beans, to assess attitude generalisation from beans previously seen to novel beans. This procedure allows one to determine the average response to novel beans, controlling for how well the individual learned positive and negative beans from the learning phase.

This task is highly innovative and is the product of many years of testing and iterative development. It addresses previous difficulties in the assessment of valence asymmetries. For example, previous tasks investigating valence asymmetries were based on stimuli consisting of affective sounds, words and pictures (Norris, Larsen, Crawford, & Cacioppo, 2011), for example a picture of a gun as a negative image, a picture of a baby of a positive image. This is problematic as often participants have highly individualised preconceived impressions of the subjective stimuli, making it extremely difficult to assess true cognitive processing biases. For example, an avid recreational shooter will find the image of a gun positive, and an overwhelmed new parent find the baby picture negative. BeanFest addresses this problem by using novel unemotive stimuli with which participants have had no previous exposure, carefully pairing them with reward or loss experiences, and thus allowing the measurement of *learning* and *formation* of affective attitudes that are untainted by past experiences or attitudes.

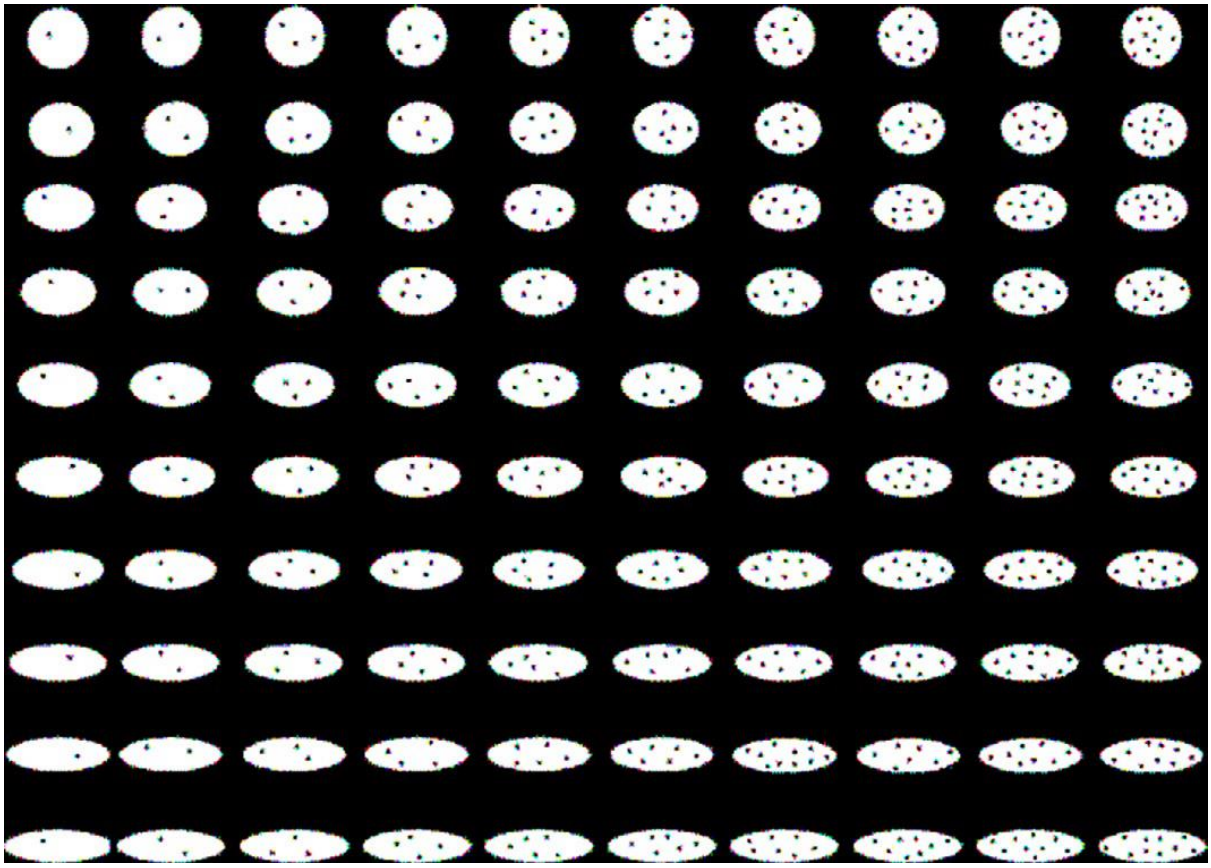

Figure 5.1.1: The bean stimuli used in the Beanfest task. Adapted from (Fazio et al., 2015).

5.1.3. Current evidence for valence asymmetries

BeanFest has shown high sensitivity to both positive and negative valance asymmetries across a large and growing body of research. For example, depressed and anxious individuals display a negative learning bias, which is driven by a lack of appreciation for the positive beans they had encounter (Conklin, Strunk, & Fazio, 2009; Shook, Fazio, & Vasey, 2007). Moreover, a negative weighting bias has been found to predict increases in depressive symptoms in university students (Pietri, Vasey, Grover, & Fazio, 2015), highlighting the tasks predicative validity for mood concerns.

Differences in weighting biases have also been linked to inter-personal relationships. Weighting bias has been shown to predict the number of new peer relationships first-year university students will form within their first two months of university, whereby a positive

weighting bias is linked to more new relationships (Rocklage, Pietri, & Fazio, 2017). A more negative weighting bias is associated with greater sensitivity to the possibility of interpersonal rejection, as well as apprehension regarding novel people and situations (Pietri, Fazio, & Shook, 2013). This suggests that valences asymmetries may impact the quality of interpersonal relationships and provide real-world indications of approach and avoidance behaviours.

Moreover, and most relevant to compulsivity, valence asymmetries have been linked to impulse control and risk tendencies. Individuals who exhibit positive valence biases on BeanFest have less impulse control than individuals who have negative valences, however this relationship only holds for individuals with low trait self-control (Zunick, Granados Samayoa, & Fazio, 2017). Similarly, those with a more positive weighting bias have a tendency to engage in riskier behaviours (Pietri et al., 2013). This indicates that those who have a more positive valence asymmetry display a greater susceptibility to disinhibition and maladaptive behaviours.

5.1.4. Valence asymmetries in experiential avoidance and compulsivity

Although yet to be investigated, cognitive valence asymmetries may contribute to compulsivity, particularly in the context of compulsive behaviour that is motivated by EA. There is good rationale to suggest an interaction between the three (i.e. compulsivity, EA and valence asymmetries). EA is linked to increased mood related concerns, such as anxiety and depression, both of which have been associated with a negative learning bias (Conklin, Strunk, & Fazio, 2009; Shook, Fazio, & Vasey, 2007). Moreover, theory of EA describes how experientially avoidant individuals have a bias towards attending to negative *internal* experiences which perpetuates avoidance behaviour. This bias may extend to negative *external* experiences, thus fostering more negative assessments of novel stimuli and avoidance behaviour.

However, compulsivity is, by nature, characterised by excessive approach behaviours, in that individuals seek out stimuli and situations (e.g. alcohol, shopping, gambling, eating, checking, counting) with the expectation that there will be a positive outcome (e.g. relieve anxiety, distract from negative thoughts). Therefore, it could be argued that compulsive individuals may have a bias towards learning positive associations. They have a greater tendency to quickly learn which situation is acutely helpful and continue to engage in that behaviour. This may come at the expense of more conscious deliberation of both the positive *and* negative associations of that behaviour. For example, drinking alcohol will acutely relieve feelings of anxiety however can have distal negative consequences, such as a hangover and feeling tired the next day.

Consider again the exercise example; an individual who has an underlying motivation to exercise *and* has positive expectations of the actual act of exercising, is more likely to exercise than someone who is motivated but had negative expectations. Therefore, someone who is motivated to avoid negative internal experiences (i.e. experientially avoidant) *and* has a positive expectation of a certain behaviours (e.g. alcohol, shopping, gambling, eating, checking, counting) may be more at risk of problematic compulsive behaviour. This is in comparison to someone who may be also motivated by EA but is aware of the negatives associated with excessive behaviours (e.g. functional impairments, time consuming etc.). Consequently, in the case of compulsivity, a negative bias may in fact be protective, as it may help the individual to associate more distal negative consequences with the compulsive behaviour rather than the immediate positives. It is important to understand the nature of the interaction between EA, valence asymmetries and compulsivity, as this may shed light on processes which protect or exacerbate compulsivity, thus guiding potential new treatment avenues. For example, if a negative weighting bias is

protective for EA-motivated compulsivity, then cognitive treatment interventions could be targeted towards adjusting positive biases towards being more neutral or negative.

5.2. HPA axis function

As outlined in earlier chapters, compulsive behaviour may be a manifestation of an imbalance between the brain's goal-directed and habit-learning systems, whereby there is a reduction in goal-directed control over behaviour and a concomitant strengthening of habit-like responding (Gillan et al., 2015). There is a large body of work linking stress to the promotion of habitual behaviour (Schwabe & Wolf, 2009; Schwabe, Tegenthoff, Höffken, & Wolf, 2013; Smeets, van Ruitenbeek, Hartogsveld, & Quaedflieg, 2019; Wirz, Wacker, Felten, Reuter, & Schwabe, 2017), suggesting that increased stress may be a vulnerability factor for compulsivity (Gillan et al., 2015; Schwabe, Dickinson, & Wolf, 2011; Stephens & Wand, 2012a). EA has a reciprocal relationship with stress, whereby EA predicts increased stress responses and increased stress leads to more experientially avoidant behaviour (Ishizu, Shimoda, & Ohtsuki, 2017). Stress and EA have also been shown to interact and increase the risk of psychopathology (Rueda & Valls, 2016). Thus, stress likely plays a key role in the onset and exacerbation of experientially avoidant compulsive behaviour

The Hypothalamic-Pituitary-Adrenal (HPA) axis functioning is a widely investigated biological indicator of stress (Stephens & Wand, 2012) and irregularities in HPA functioning are closely tied to affective processing and emotion regulation disruptions (Bao & Swaab, 2019; Gilbert, Mineka, Zinbarg, Craske, & Adam, 2017). The HPA axis allows us to maintain daily function under changing environmental circumstances (Herman et al., 2016). The product of the HPA system is cortisol, which plays a role in the maintenance of homeostasis and the fine balanced regulation of stress. Changes in cortisol levels outside of homeostatic basal secretion are triggered by stressors in the environment. The axis is regulated through negative feedback, whereby hippocampal structures exert inhibitory influences on the axis,

while the amygdala typically plays an axis-activating role (Herman et al., 2016). HPA activity is an important mediator between stressful life experiences and mental health outcomes (Renoir, Hasebe, & Gray, 2013), thus it may help to explain why some individuals who experience negative emotions (e.g. stress) go on to engage in compulsive behaviour.

Notably, alterations in HPA axis regulation constitute a risk factor for problematic alcohol use, whereby cortisol interacts with the brains rewards systems to promote alcohol's reinforcing effects and increase habit-learning (Stephens & Wand, 2012). In comparison to healthy controls, abnormalities in HPA axis activity and cortisol production have also been found in patients with OCD and binge eating disorder (Morgado, Freitas, Bessa, Sousa, & Cerqueira, 2013; Rosenberg et al., 2013), supporting the role of HPA axis activity in compulsive behaviour.

5.2.1. Characterisation of HPA-axis activity

Although there are several biomarkers, such as the corticotropin-releasing or adrenocorticotropic hormones, which can provide indication of HPA axis activity, cortisol is most widely used in health psychology literature as it can be measured without undue inconvenience or risk to participants and does not require specialised medical personnel (Nicolson, 2008). HPA activity, and therefore cortisol secretion, has a pronounced circadian rhythm (Hucklebridge, Hussain, Evans, & Clow, 2005). There are several approaches to characterising individual differences in patterns of cortisol secretion. However, assessment across multiple levels is often not feasible in research studies, due to costs, time burden and the intrusive nature of some procedures. The main approaches for determining cortisol levels include measuring basal cortisol production, diurnal pattern of cortisol secretion, cortisol reactivity in response to acute stressors and the cortisol awakening response (CAR). Although all approaches are valid ways to assess HPA axis activity, the CAR is associated with the lowest participant and researcher burden (Nicolson, 2008). Other approaches

involve multiple collection times across a 24-hour period or require increasing participant stress. The CAR is the primary biomarker used in the current thesis and thus will be the focus of subsequent discussion.

5.2.2. Measurement of the Cortisol Awakening Response

Cortisol awakening response (CAR): The CAR is the steep rise (~50-160%) in cortisol during the first 30 – 40 minutes of awakening, returning to baseline after 60 – 75 minutes and continuing thereafter (Nicolson, 2008). Measurement of the CAR only requires a brief period (~ 60 minutes) of saliva sampling in the morning, making is a widely used measure of HPA function in health psychology literature. However, despite its wide use, there is considerable inconsistency within the literature over how CAR should be measured. This is particularly problematic as the validity of the CAR critically relies on appropriate measurement procedures. In favour of succinctness and clarity, the thesis publication (Study Two; Chapter 7) which utilised CAR data did not contain a detailed description of the CAR measurement protocol. As such, pertinent decisions relating to the protocol that could not be detailed in the publication will be discussed here.

Urinary, blood or salivary cortisol: While the CAR can be measured through urinary or blood collection, it is most commonly measured through saliva sampling. Although blood and urinary cortisol are typically found in higher concentrations and the quality of the sample is less vulnerable to extraneous factors (El-Farhan, Rees, & Evans, 2017), saliva sampling is preferred due to feasibility. Saliva sampling is advantageous as it reduces participant burden and invasiveness, with ease of collection largely contributing to its popularity in research. Moreover, there is generally high agreement (> .90) between salivary and blood plasma concentrations, further supporting the use of salivary cortisol (Kirschbaum & Hellhammer, 2007). The ease of collection was an important consideration in the current thesis. As we were collecting data across several different modalities, we sought

to reduce participant and researcher burden where possible, without significantly diminishing the quality of the research. Therefore, given its good agreement with urinary and blood cortisol, and reduced burden of collection, salivary cortisol was used to characterise the CAR.

Assessment of the cortisol awakening response: In 2016, expert consensus guidelines were published describing gold standard procedures for the assessment of the CAR (Stalder et al., 2016). The guidelines outline several important considerations related to the control of the sampling accuracy; participant instructions; influence of covariances; assessment of the CAR; and data reporting and interpretation. These guidelines informed CAR assessment protocol in the current thesis. Key decisions made based on the guidelines are outlined below.

The guidelines recommend at least three time points within the first hour of awakening should be collected, suggesting sampling at 0 min (i.e. on awakening), 30 min and 45 min. Many studies use only two time points, likely due to feasibility and cost limitations. However, leading researchers in the field argue that a minimum of three time points (e.g. 0 min, 30 min and 45 min) should be collected to allow sufficient characterisation of the curve (Clow, Thorn, Evans, & Hucklebridge, 2004; Angela Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; P. Evans, Smyth, Thorn, Hucklebridge, & Clow, 2019). In addition, the CAR should be measured on multiple days to account for day to day variability between samples. While up to six consecutive days is ideal, this is recognised as impractical and a minimum of two days is recommended.

Studies have shown that people are generally adherent to the sampling protocol (Hill Golden et al., 2014; Thorn, Hucklebridge, Evans, & Clow, 2006), however, researchers advise the use of quality control measures such as sleep actigraphy equipment to confirm that the "waking" sample was collected at the actual wake time (Stalder et al., 2016). Errors in

sampling times can have significant impacts on the validity of the CAR. For instance, if the "waking" sample (0 min) is delayed, the CAR may have already commenced, leading to an incorrect characterisation of the curve and its peak.

Although ideal, such equipment is expensive and was not feasible in the current research, due to costs and already high participant burden. Alternatively, researchers can check the quality of data at the analysis stage. If the concentration of cortisol is greater at time 0 min when compared to times 30 or 45 min, then this is an indication that there was a delay in wake time collection. While a higher 0 time point may be expected in severe clinical populations (Stalder et al., 2016), it is not typically seen in community-based samples as used in the current research.

Finally, the guidelines provide considerations for CAR data reporting and interpretation. This includes reporting the cortisol concentration of the first sample for each of the groups and a measure of dynamic cortisol increase, such as the mean increase in cortisol from awakening. In a more recent publication since the guidelines, another method for analysing CAR was identified, referred to as the CAR salience score (Evans et al., 2019). This was shown to perform significantly better than traditional CAR calculations (e.g. area under the curve (AUCi) or mean increase (MnInc) from awakening) at revealing more trait-like individual differences (Evans et al., 2019) and was the measure of dynamic increase utilised in the current thesis.

5.2.3. The cortisol awakening response in experiential avoidance and compulsivity

One prominent theory about the function of the CAR is that it may be an anticipatory response, preparing the individual to cope with the demands of the upcoming day (Fries, Dettenborn, & Kirschbaum, 2009; Powell & Schlotz, 2012). This theory is born out of research showing a heightened response in relation to short-term influences such as a stressful workday compared to a weekend (Kunz-Ebrecht et al 2004). Research directly

testing this “anticipation” theory has found the CAR moderates the effect of daily life stress on distress, whereby CAR increases are associated with reduced distress responses to daily life stress (Powell & Schlotz, 2012). This suggests that CAR elevation is linked to better ability to cope with stress. This is an important finding in the context of EA and compulsivity. As has been discussed in previous chapters, when considering compulsive behaviour within the framework of EA, compulsivity can be conceptualised as a poor coping strategy for distress. Given that a higher CAR is linked to better coping with distress, one may anticipate that individuals who are experientially avoidant and compulsive to have an attenuated CAR.

Although the above implies that a greater CAR is a protective factor for coping with stress, other research findings have identified a heightened CAR as a biomarker of negative mental health outcomes. For instance, feelings of threat, sadness and lack of control have been show to predict a larger CAR the following day (Adam, Hawkley, Kudielka, & Cacioppo, 2006). Moreover, in a meta-analysis of more than 140 studies, CAR was found to be heightened among people reporting worry or preoccupation with their work and generally elevated in those experiencing chronic stress and work-overload (Chida & Steptoe, 2009). Of note, when there is a reduction in life stressors, this is accompanied by a decrease in the CAR, demonstrating a relationship between changes in stress and the magnitude of the CAR (Andrew Steptoe, Brydon, & Kunz-Ebrecht, 2005). Therefore, an increased CAR appears to reflect the body preparing to actively cope with stress (Powell & Schlotz, 2012).

Research investigating the CAR in disorders of compulsivity has elicited mixed findings. For instance, women with binge eating disorder have a significantly elevated CAR in comparison to healthy women (Monteleone et al., 2016). However, in a community-based sample, the CAR was negatively associated with binge-eating behaviours and disinhibition (Therrien et al., 2008), suggesting an increased capacity to disinhibit could be the result of increased HPA activity. This finding is broadly consistent with the anticipation

theory of the CAR, which suggests a higher CAR is linked to better ability to cope day-to-day. Problem gamblers also exhibit an elevated CAR, however this is not related to individual differences in disinhibition (Wohl, Matheson, Young, & Anisman, 2008), leading authors to conclude an elevated CAR is secondary to gambling problems or distress related to gambling problems. The relationship between compulsivity and the CAR is complex and seems to function differentially depending on disorder severity (i.e. community sample versus clinical sample). In mild-moderate symptoms severity populations, it is possible an elevated CAR serves a protective role, encouraging greater self-control. While in severe population groups, CAR may be more indicative of pathological distress-related behaviours.

5.3. Amygdala function

As outlined in Chapter 2, several brain regions have been implicated in explaining compulsive behaviour, including various regions in CSTC and limbic circuitry. Here, the amygdala was raised as an area of interest within the context of its role in negative reinforcement and stress. As the current thesis is conceptualising compulsive behaviour as an expression of experientially avoidant behaviour and disrupted affective processing, the amygdala is an important brain region for further investigation, given its known role in affect generation and regulation.

The amygdala is a subcortical, bilateral structure, located within the medial temporal lobe (AbuHasan & Siddiqui, 2020). It receives diverse inputs and outputs from various cortical and subcortical regions of the brain, which underlie many affect-related processes. For instance, bottom-up connections between the amygdala and regions such as the insula, striatum and visual cortex guide attention and perception of emotional stimuli in the environment (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). The amygdala generally plays a modulatory role in bottom-up processes, directing attention and flagging the salience of emotional stimuli (Lindquist et al., 2012). Top-down systems, which include

connections between the amygdala with regions in the frontal cortex, parietal cortex, ACC and hippocampus, are thought to be involved in the regulation of emotion and re-appraisal of emotional stimuli (Ochsner et al., 2009). Here, top-down cortical and subcortical systems exert modulatory control over the amygdala.

Interactions among large-scale brain-networks and the amygdala engender many of the psychological and cognitive processes involved in affective processing (Jacobs et al., 2016; Jenkins et al., 2017; Uchida et al., 2015). A recent meta-analytic review identified five networks thought to interact with the amygdala in affective processing (Riedel et al., 2018). These comprised two networks associated with visual and auditory perception, and three linked to higher-order functions including attention for emotionally salient stimuli, internal representations of past emotional stimuli, and emotional stimulus evaluation and response generation. Higher-order functions were associated with well-known large-scale networks including the salience network, default mode network (DMN) and limbic network respectively. Therefore, while the amygdala plays a crucial role in affective processing, it is important to move beyond investigating the amygdala as a single region, towards investigations aimed at understanding how brain networks interact with the amygdala to produce affect driven behaviour.

5.3.1. Measurement of amygdala function

Functional magnetic resonance imaging (fMRI) studies are used to understand how brain regions interact with each other and within a network. These can either be task-based fMRI (i.e. measure brain activity while performing a specific cognitive function) or resting-state-fMRI investigations (i.e. measure activity while the brain is at rest). Task-based studies, which tend to be more widely used, allow researchers to measure brain regions that are active during specific behaviours and thus elucidate the function of various networks and connections. For example, greater functional connectivity between the amygdala and PFC is

observed during exposure to unpredictable threat in a computer-based paradigm (Gold, Morey, & McCarthy, 2015), leading to the interpretation that amygdala-PFC connectivity is important to help maintain performance when experiencing anxiety induced by threat. Although task-based fMRI studies provide valuable insights into the function of various network connections, they are limited in that they focus on one behaviour as measured by a specific cognitive task and the real-world applicability of tasks is at times questionable. Resting-state investigations are advantageous as they provide insight into experience-dependent (i.e. real-world rather than task-based) functional and structural organisation of the brain, allowing for identification of wider network dysregulation and abnormalities in pathological behaviour. Researchers suggest that rs-FC reflects the underlying synaptic efficiencies (or metabolic expenditure) in cortical networks (Guerra-Carrillo, Mackey, & Bunge, 2014). For example, amygdala rs-FC to other regions throughout the brain tends to be decreased in depression (Ramasubbu et al., 2014), lending weight to neurobiological modes of depression and suggesting that emotion regulation difficulties is depression can be (in part) attributed to a dysregulated brain circuitry.

5.3.2. Amygdala function in experiential avoidance and compulsivity

Despite the likely relevance of amygdala function in compulsivity, and potential for rs-FC assessment to provide insight into underlying amygdala network function in this population, very few investigations have explored amygdala rs-FC in the context of compulsive behaviour. In the following sections I will briefly summarize the current understanding of amygdala function within the context of compulsive behaviours. The focus will be on resting-state investigations, as this will directly inform the current thesis research studies. However, where necessary the discussion will draw upon findings from task-based investigations to illustrate network function.

Amygdala function in OCD: Traditional neurobiological models of OCD attribute symptom presentation to underlying dysfunction of CSTC loops (for review see Hazari, Narayanaswamy, & Venkatasubramanian, 2019), however recent evidence also implicates other networks, such as limbic networks and the amygdala (Via et al., 2014). Abnormalities in limbic network activity likely underlie affect regulation difficulties observed in OCD (Göttlich, Krämer, Kordon, Hohagen, & Zurowski, 2014), including performance of compulsions in response to feelings of uncertainty and/or anxiety.

Resting-state investigations have found evidence of amygdala network dysregulation in OCD. Decreased functional connectivity between the amygdala and prefrontal regions at rest suggests reduced efficiency of communication between areas involved in adaptive emotional learning (Fullana et al., 2017). Similarly, reduced rs-FC between the amygdala and the basal ganglia network (inclusive of the dorsal and ventral striatum) and the executive/attention network (inclusive of fronto-parietal regions) are thought to contribute to OCD cognitive deficits in emotional learning, processing and expectation, as well as processing of rewards and punishments (Göttlich et al., 2014). Of note, structural changes in the amygdala have also been observed in subclinical obsessive-compulsive groups, suggesting amygdala neuronal changes may constitute a risk factor for obsessive-compulsive behaviour, rather than simply being a consequence of psychopathology (Kubota et al., 2019).

Amygdala function in substance addictions: Early work exploring the neurocircuitry of addictive behaviour has implicated the amygdala and its functional connections throughout the brain (Koob & Volkow, 2010). Specifically the amygdala plays a key role in the negative affect/withdrawal stage of addiction and is thought to be a neural marker for addiction driven by stress and negative affective states (Koob & Le Moal, 2008). Although a range of different substances lend themselves to addiction, here the discussion will

primarily focus on alcohol use problems, as this is the substance-related behaviour that informs the research investigations of the current thesis. Alcohol was chosen as the substance of focus because it is the most widely used substance worldwide (Degenhardt et al., 2018).

Reduced amygdala connectivity to frontal regions, such as the OFC, have been shown to predict alcohol use two years later in adolescents, suggesting that decreased amygdala-frontal connectivity at rest may bias individuals towards more risk-taking behaviours later on (Peters, Peper, Van Duijvenvoorde, Braams, & Crone, 2017). Similar findings are also observed in adults, whereby there is decreased rs-FC connectivity between the amygdala and cognitive control regions (Hu et al., 2018). By comparison, amygdala connectivity to striatal reward regions is increased in alcohol use disorder (Zhu, Cortes, Mathur, Tomasi, & Momenan, 2017), possibly reflecting hyperactivity between systems implicated in affective motivation and reinforcement relevant to addictive behaviour.

Amygdala function in behavioural addictions: Very few studies have investigated amygdala functional connectivity (both at rest and during task) in behavioural addictions. However, there is good rationale to support its role. Pathological overeating identifies "overeating to relieve a negative emotional state" as one of the key driving processes (Moore, Sabino, Koob, & Cottone, 2017, p. 1378). This is supported by research showing negative affect tends to increase and positive affect decrease prior to a binge eating episode (Wonderlich et al., 2018). Performing a behaviour to relieve an emotional state is thought to emerge from dysfunction within the amygdala (Moore et al., 2017). Moreover, evidence has shown that the amygdala is hyperactivated in response to pleasant tasting food, even when someone is not hungry (Sun et al., 2015) and activates in response to high-calorie foods in food addiction (Pursey, Contreras-Rodriguez, Collins, Stanwell, & Burrows, 2019). Thus, this

suggests greater amygdala-related motivational sensitivity to palatable foods may contribute to compulsive eating behaviours.

Individuals who gamble demonstrate increased engagement of amygdala-striatal networks when making choices about whether to quite or continue chasing losses (Worhunsky, Potenza, & Rogers, 2017), indicating affective and reward-based systems of the brain are influencing decisions about gambling continuation rather than higher-order cognitive control regions. Increased amygdala connectivity with other regions involved in emotional salience and generation, such as the insula, have also been observed in pathological gambling (Contreras-Rodríguez et al., 2016), suggesting the brain may hyper-sensitive towards affective responses.

Amygdala function in experiential avoidance: Only two studies have explicitly investigated brain function associated with EA. Using a small pilot sample of 16 healthy adults, one study mapped approach and avoidance responses during a monetary gains computer task to increased fronto-limbic-striatal network activation (inclusive of medial/superior frontal regions, anterior cingulate, amygdala and hippocampus). Increased EA (self-report) was found to be associated with decreased activation within this network, suggesting EA is linked to poorer communication (or connectivity) between key regions responsible for modulating approach/avoidance behaviour (Schlund, Magee, & Hudgins, 2011). This may reflect decreased cortical control over limbic regions in EA and thus an imbalance between habitual/automatic responding over reflective/cognitive control responding.

The same research team attempted to extend upon this finding using another small sample (17 healthy adults), investigating the relationship between EA and activation within emotion-related brain regions during a sustained threat avoidance task (Schlund, Hudgins, Magee, & Dymond, 2013). Interestingly, results showed EA was linked to decreased

activation within limbic regions (i.e. amygdala, insula, substantia nigra and bed nucleus of the stria terminalis complex) during initial threat exposure on the task, although not over sustained threat exposure. This finding seems somewhat counterintuitive, as one would expect increased limbic activation in response to threat in EA. Authors interpreted the findings as individuals with increased EA being less threatened by monetary loss (as compared to unwanted emotions) or extensive histories of avoidance based coping creating some resilience to threat/ lower threat sensitivity. Although this preliminary evidence is promising and suggests a relationship between EA and limbic activation, the available work is limited, both in terms of the number of studies and sample sizes.

Overall, there is emerging evidence to indicate disrupted amygdala connectivity with higher-order control and sub-cortical reward-based areas of the brain contributes to behaviour presentation in compulsivity. Reduced brain-based capacity for affect regulation and heightened affective responses likely leads to an overreliance on accessible and acutely effective behaviours (e.g. eating, drinking, gambling, cleaning etc.) to manage emotions. As was outlined in earlier chapters, disruptions to CSTC neurocircuits and their related processes can explain a portion of the variance in compulsive behaviour, suggesting there are intermediate phenotypes (also referred to as endophenotypes) that can explain symptom variation across multiple compulsive behaviours and likely a fraction of the commonly observed comorbidities. Based on the emerging evidence into amygdala function in compulsivity, it is also likely there are phenotypes of compulsive behaviour that can be explained by amygdala neurocircuitry and its related processes. However, at this stage, such conclusions are largely speculative given the limited studies conducted and the absence of any transdiagnostic investigations exploring amygdala rs-FC in compulsivity.

5.4 Investigating "hidden" phenotypes using multidimensional indicators

Given the mounting evidence demonstrating that diagnostic categories do not capture the underlying neurobiology of mental illness (Chamberlain, Stochl, Redden, & Grant, 2018; Chamberlain et al., 2019; Fontenelle, Oostermeijer, Harrison, Pantelis, & Yücel, 2011; Hermens et al., 2019; Parkes et al., 2019; Tiego, Oostermeijer, et al., 2019b), researchers are being encouraged to explore empirically-based approaches for re-classifying psychopathology, grounded in findings from neuroscience (Cuthbert & Insel, 2013). The current thesis sought to reclassify heterogeneous compulsive behaviours, incorporating multiple levels of analysis (i.e. EA, stress, valence learning asymmetries, CAR and amygdala rs-FC). Data-driven clustering offers a promising empirical approach for discovering "hidden" transdiagnostic phenotypes based on multidimensional indicators. Clustering uses machine learning algorithms to identify patterns within data in the absence of group labels (e.g. disorder groups). This approach has already demonstrated promise in other areas of psychopathology, identifying common neurobiological profiles in previously heterogeneous conditions including psychosis (Clementz et al., 2016), mood-related disorders (Grisanzio et al., 2018; Tokuda et al., 2018) and panic disorders (Pattyn et al., 2015).

For example, Clementz & colleagues (2016) utilised a broad range of cognitive indicators to form three distinctive "biotypes" of psychosis which were differentiated on levels of cognitive control and sensorimotor function. Biotype one showed severe deficits on both levels of function, biotype two exhibited deficits only on cognitive control, and biotype three demonstrated the least impairment. Biotypes mapped onto brain neuroanatomy, with biotype one exhibiting the most widespread gray matter reductions throughout the brain, while biotype two had similar reductions albeit less pronounced and biotype three exhibited the most modest reductions that were relatively localised to limbic brain regions (*Figure 5.4.1)*. Comparatively, DSM diagnostic categories (i.e. schizophrenia versus schizoaffective

disorder) were statistically indistinguishable in brain structure, suggesting the biotypes were superior to DSM categories at capturing neurobiological distinctiveness. Importantly, biotypes spanned across conventional diagnoses, thus lending support to a transdiagnostic conceptualization of psychosis symptoms. Alongside offering a novel way to reclassify mental disorders (one that is based in research science) and providing insight into how distinct functional systems interact in psychopathology, this approach also generates new considerations for guiding research interventions and outcomes. For instance, based on the biotype profiles authors suggested biotype three could inform explorations of psychosis risk, while treatments for biotype one should be directed to compromised cognitive control and correcting sensorimotor disruptions.

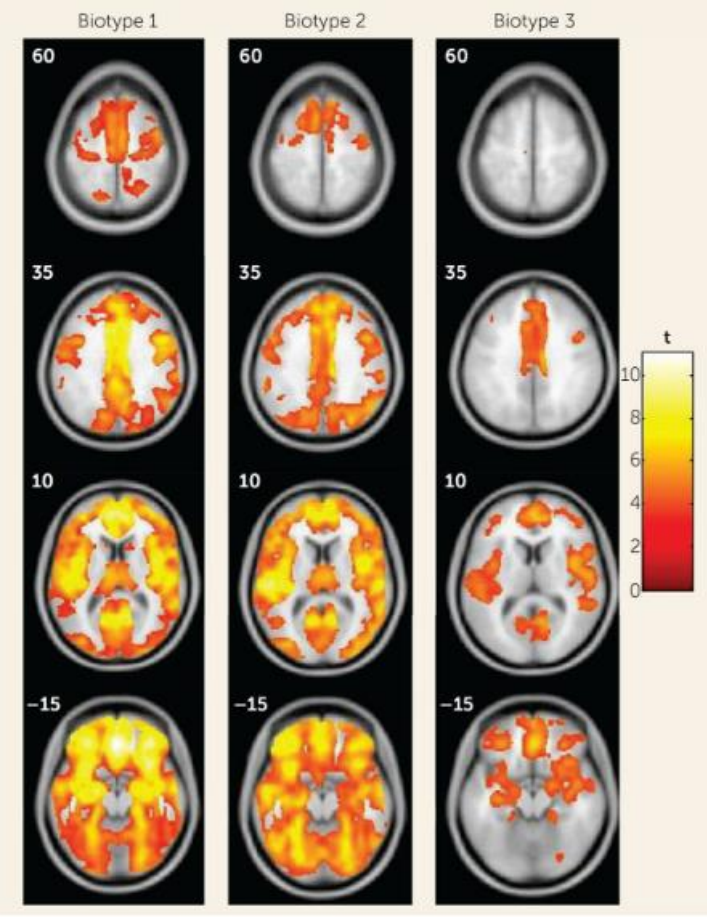

Figure 5.4.1. Gray matter differences in biotypes one, two and three. Biotype one exhibiting the most widespread gray matter reductions, biotype two had similar reductions

albeit less pronounced and biotype three exhibited the most modest reductions that were relatively localised to limbic brain regions. Figure adapted from (Clementz et al., 2016).

More recently, Grisanzio & colleagues (2018) applied a similar approach to explore transdiagnostic affect-related symptoms across multiple levels of function. Participants either had a primary diagnosis of major depression, panic disorder, post-traumatic stress disorder or no disorder (healthy controls). From this, researchers identified six distinct subtypes that were clinically relevant and differentially expressed on measures of cognitive control, working memory, electroencephalography (EEG) brain activation at rest and during an emotional paradigm, social functioning and resilience. For example, the "anxious arousal" subtype was distinguished by poor daily functioning and the greatest level of cognitive impairment, while the "general anxiety" subtype was characterized by elevated emotion-elicited brain activation, mildly reduced working memory and intact daily function. These subtypes also existed across diagnostic labels, thus lending support to a transdiagnostic conceptualization of mood symptoms.

This work demonstrates multidimensional indicators related to affect can be used to identify hidden phenotypes. However, unlike work by Clementz & colleagues (2016), this investigation did not evaluate the neurobiological validity of phenotypes using brain imaging measures. There is often considerable variability associated with cognitive and biological data. Therefore, when data-driven clustering is applied to this data, it may yield phenotypes that are unrelated to psychiatric pathology and instead reflect nuisance variance associated with the data (Dinga et al., 2019). On way to overcome this limitation is to assess the neurobiological validity of the phenotypes, by examining for meaningful brain-based differences between phenotypes, as was done by Clementz & colleagues (2016). Study Two (Chapter 7) of the current thesis utilises a similar data-driven approach to reclassify

heterogenous compulsive behaviours and assesses the neurobiological validity of discovered phenotypes using amygdala-based resting-state fMRI. Identifying novel and biologically meaningful phenotypes has the potential to inspire new and specific theories of compulsivity that could be further investigated.

CHAPTER SIX

6. Study One: The role of Experiential Avoidance in Transdiagnostic Compulsive Behaviour: A Structural Model Analysis

6.1. Introductory comments

This chapter presents a research article entitled "The role of Experiential Avoidance in Transdiagnostic Compulsive Behaviour: A Structural Model Analysis", which has been accepted for publication by the Journal of Addictive Behaviors. This study focussed on transdiagnostic compulsive behaviours within the community and determining whether there was association between compulsivity and EA.

A novel method was utilised to assess compulsive behaviour, whereby diagnostically accepted behaviours related to OCD (i.e. cleaning, checking for harm and achieving symmetry), alcohol addiction and gambling addiction, as well as emerging concepts of eating and shopping addiction were assessed using adapted versions of the Yale-Brown Obsessive-Compulsive scale. These behaviours were chosen to encompass both common OCD- and addiction-related behaviours. For the addiction related behaviours, we sought to include a spread of subtypes (i.e. substance, behavioural and non-diagnostic behavioural). Although other prevalent behaviours such as internet/ gaming/ social networking could be conceptualized as compulsive behaviours, the exact nature and status of internet-related behaviours is not yet clear (Ioannidis et al., 2016) and there may be subtypes embedded within the problematic internet use continuum (Tiego, Lochner, et al., 2019). Therefore, we selected domains where the nature of the behaviour was well defined and understood. This is the first-time compulsivity has been assessed using adapted Y-BOCS. This approach is advantageous as it allows for a broad range of behaviours to be captured on the same

measurement scale, providing an overall indication of compulsive thoughts and behavioural patterns irrespective of the type of behaviour.

The nature of the relationship between compulsivity and EA was empirically tested using a sophisticated statistical technique called Structural Equation Modelling (SEM). Structural equation modelling (SEM) is a multivariate statistical analysis method which allows one to investigate complex path models with latent (i.e. underlying factors, not directly observed) and indicator (i.e. single variables, observed) variables. Using this approach, we attempted to delineate the processes through with EA and distress influence transdiagnostic compulsive behaviour.

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The role of Experiential Avoidance in transdiagnostic compulsive behavior: A structural model analysis

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HIGHLIGHTS

- Compulsive behaviors are prevalent within the general community.
- Our results support a transdiagnostic conceptualization of compulsive behavior.
- Experiential avoidance in the context of distress predicts increased compulsivity.

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ABSTRACT

Compulsivity is recognized as a transdiagnostic phenotype, underlying a variety of addictive and obsessive–compulsive behaviors. However, current understanding of how it should be operationalized and the processes contributing to its development and maintenance is limited. The present study investigated if there was a relationship between the affective process Experiential Avoidance (EA), an unwillingness to tolerate negative internal experiences, and the frequency and severity of transdiagnostic compulsive behaviors. A large sample of adults (N = 469) completed online questionnaires measuring EA, psychological distress and the severity of seven obsessive–compulsive and addiction-related behaviors. Using structural equation modelling, results indicated a one-factor model of compulsivity was superior to the two-factor model (addictive- vs OCD-related behaviors). The effect of EA on compulsivity was fully mediated by psychological distress, which in turn had a strong direct effect on compulsivity. This suggests distress is a key mechanism in explaining why people with high EA are more prone to compulsive behaviors. The final model explained 41% of the variance in compulsivity, underscoring the importance of these constructs as likely risk and maintenance factors for compulsive behavior. Implications for designing effective psychological interventions for compulsivity are discussed.

1. Introduction

Maladaptive behaviors, such as problem gambling, binge-eating and compulsive shopping, share considerable phenotypic and neurobiological overlap with substance addiction, and thus have been argued to represent 'behavioral addictions' (Gordon, Ariel-Donges, Bauman, & Merlo, 2018; Mann, Fauth-Bühler, Higuchi, Potenza, & Saunders, 2016; Trotzke, Brand, & Starcke, 2017). Researchers also liken aspects of obsessive–compulsive disorder (OCD) to a behavioral addiction, given the similarities between the compulsive characteristics of OCD and the cognitive and behavioral characteristics of addiction (Grassi & Pallanti, 2017). For example, obsessive–compulsive behaviors may be driven by a need for immediate gratification, despite future consequences, as opposed to risk aversion (Grassi et al., 2015). Importantly, substance addiction, behavioral addictions and OCD share overlapping pathogenic mechanisms across multiple levels of analysis including phenomenology, symptom, cognitive and neurobiological (Figee et al., 2016; Fontenelle, Oostermeijer, Harrison, Pantelis, & Yücel, 2011), suggesting they may reflect different manifestations of common etiology.

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Research has recently shifted focus from categorical to a dimensional understanding of psychopathology, whereby symptoms vary along a spectrum of severity extending into the non-clinical range and may reflect the expression of underlying dimensional phenotypes (Kotov et al., 2017; Krueger & Deyoung, 2016). The phenotype of 'Compulsivity' is relevant for understanding and treating OCD and addictions (Fineberg, Menchon, Zohar, & Veltman, 2016). It is defined by repetitive, habitual and functionally impairing behaviors that are difficult to control (Figee et al., 2016; Robbins, Gillan, Smith, de Wit, & Ersche, 2012; Voon et al., 2015) and are often preceded by a feeling that they have to be performed (Luigjes et al., 2019). Compulsivity also exists outside psychiatric diagnoses with problematic behavior evident at subclinical and community-based levels (Chamberlain, Stochl, Redden, & Grant, 2018; Chamberlain et al., 2019). Our recent work has shown that compulsivity is a dimensional phenotype, measurable in both general and clinical populations, and that transdiagnostic measures of compulsivity better explain individual variance at both symptom and neurobiological levels compared to traditional diagnostic labels of OCD and addiction (Parkes et al., 2019; Tiego et al., 2019). Although compulsivity is gaining considerable research interest, our current understanding of how it should be operationalized, and the underlying mechanisms contributing to its development and maintenance, remains limited. Understanding the nature of these processes is essential in identifying markers for pathological behavior (Venkatasubramanian & Keshavan, 2016) and for the development of more effective transdiagnostic interventions for chronic illnesses such as addiction (Borsboom et al., 2016).

1.1. Experiential Avoidance as motivator for compulsive behavior

One potentially potent psychological motivator of compulsive behaviors which has not yet been investigated is Experiential Avoidance (EA). EA is an affect-related regulatory process, whereby individuals are unwilling to remain in contact with negative internal experiences (i.e. thoughts, emotions) and are motivated to alter or avoid these experiences (Hayes, Wilson, Gifford, Follette, & Strosahl, 1996). Longitudinal studies show that EA exacerbates distress and promotes poor coping strategies (Kelly et al., 2019; Spinhoven, Drost, de Rooij, van Hemert, & Penninx, 2014; Spinhoven, van Hemert, & Penninx, 2017). There is good reasoning to suggest EA is relevant for understanding compulsive behaviors. Individuals who are experientially avoidant seek short-term relief from negative emotions (e.g. anxiety, stress), and behaviors which are vulnerable to excess (e.g. checking, alcohol-use, gambling, shopping, eating) provide effective strategies to achieve this relief. Whilst adaptive in the short-term, this process tends to be maladaptive long-term and is generally associated with lower quality of life and worse psychological well-being (Hayes et al., 2004).

Surprisingly few studies have investigated the relationship between EA and compulsive behaviors and available findings have elicited mixed results. Higher levels of EA have been linked to increased symptom severity in OCD (Wetterneck, Steinberg, & Hart, 2014), problematic alcohol use (Dvorak, Arens, Kuvaas, Williams, & Kilwein, 2013), compulsive buying (Williams, 2012), emotional eating (Litwin, Goldbacher, Cardaciotto, & Gambrel, 2017) and problem gambling (Riley, 2014). However, other research has found that EA does not significantly explain symptom presentation (Abramowitz, Lackey, & Wheaton, 2009; Manos et al., 2010). Variability in the conceptualization and measurement of EA has likely contributed to inconsistencies in findings.

Research generally conceptualizes EA as an avoidance strategy (i.e. state-based), and has found it mediates the relationship between risk factors (i.e. trauma and tendency for negative affect) and problem behavior (e.g. drug use, binge-eating, aggression; Kingston, Clarke, & Remington, 2010). More recently however, EA has been viewed as a trait-like characteristic (Kirk, Meyer, Whisman, Deacon, & Arch, 2019), represented by an unwillingness to tolerate negative emotions which in turn influences avoidant behavior across a variety of contexts that elicit distress. This perspective is reflected in newer measures of EA, which now assess it as a trait-like function (Gámez et al., 2013; Gámez, Chmielewski, Kotov, Ruggero, & Watson, 2011). Due to the variability in available literature, the role of EA and its relationship with compulsive behavior remains conceptually and statistically unclear. Moreover, very few studies have investigated compulsive behaviors using updated measures of EA (Dvorak et al., 2013; Litwin et al., 2017) and no research has explored this relationship transdiagnostically, across multiple compulsive behaviors at a time.

1.2. The present study

The present study utilized large-scale online recruitment, an approach now widely adopted in psychological research (Gillan & Daw, 2016), as it allows recruitment of more demographically diverse samples. Importantly, as majority of individuals with obsessive–compulsive and addiction-related behaviors are not in clinical care (Lipari, Hedden, & Hughes, 2013; Subramaniam, Abdin, Vaingankar, & Chong, 2012; Suurvali, Hodgins, Toneatto, & Cunningham, 2008; Torres et al., 2007) or are exhibiting problematic behavior at a subclinical level (Grabe et al., 2000; Rehm et al., 2017; Weinstock, April, & Kallmi, 2017), there is a necessity to investigate 'general population' samples. Examining vulnerable or at-risk groups who engage in compulsive behaviours has significant implications for early intervention and the need to advance our understanding of subclinical or undiagnosed OCD- and addiction-related behaviours in the community is paramount.

Using structural equation modelling, the present study first sought to test if a range of addictive behaviors (i.e. checking for harm, symmetry, contamination, gambling, eating, shopping and consuming alcohol) were better conceptualized under the model of compulsivity as opposed to traditional diagnostic categories. Within an online community sample, we examined individuals' level of compulsivity across multiple behaviors, to provide an overall, cumulative profile of compulsive behavior, expecting that if an individual had a tendency toward compulsivity this would manifest across a number of behaviors.

This study was also designed to understand affective processes that may contribute to the development and maintenance of compulsivity, and thus addictive behavior. Specifically, we sought to delineate the pathways through which EA may relate to transdiagnostic compulsive behavior. Consistent with the view that EA is a trait-like characteristic, we hypothesized that EA would positively predict compulsive behaviors. Moreover, we anticipated that this relationship would be mediated by psychological distress, as the presence of distress is likely to explain why individuals who are experientially avoidant engage in compulsive behaviors. As EA tends to paradoxically increase the frequency and severity of negative emotions (Rochefort, Baldwin, & Chmielewski, 2018; Sahdra, Ciarrochi, Parker, & Scrucca, 2016), it was thought that EA would predict increased distress. Finally, as EA itself could plausibly function as mediator or moderator, alternative models were assessed to evaluate which best explained the relationship between EA and compulsive behaviors.

2. Methods

2.1. Participants

492 participants were recruited through the Amazon Mechanical Turk (AMT) online community, aged between 18 and 50 years and with self-reported English proficiency. Participants were reimbursed $8 (USD). All experiments were performed in accordance with relevant guidelines and regulations of Monash University Human Research Ethics (Approval Number 8239).

2.2. Procedure

AMT is an online crowdsourcing platform used to collect 'big data'. It is empirically tested and validated for conducting research (Buhrmester, Kwang, & Gosling, 2011) and has been endorsed specifically for dimensional psychiatry (Gillan & Daw, 2016). Restricting recruitment to users with > 95% approval rating yields high quality data for research (Peer, Vosgerau, & Acquisti, 2014). Data quality is further enhanced through validity questions and post-hoc removal of individuals who completed jobs within implausible timeframes. The current study took approximately 60 min to complete.

2.3. Measures

2.3.1. Demographic information

Participants were asked to provide basic demographic information including relationship status, employment and income, education and any current or past mental health diagnoses.

2.3.2. Assessment of compulsive behaviors

Compulsive behavior was assessed in domains of gambling, eating, checking for harm, symmetry, contamination, shopping and consuming alcohol. These were chosen to encompass common OCD- and addiction-related behaviors. For OCD-related behaviors, checking for harm included repeatedly performing activities to prevent and check harm hasn't occurred, symmetry included re-doing activities until things felt 'just right' and contamination included washing and cleaning to prevent contamination. For addiction behaviors, we included one related to substances (i.e. alcohol), two well-established behavioral (i.e. gambling and binge-eating) and an emerging non-diagnostic behavior (i.e. shopping). Adapted versions of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, 1989) were tailored to measure transdiagnostic compulsivity in each of the domains (detailed in Supplement). The Y-BOCS has previously been adapted to measure addiction behaviors (Fedoroff, Sobell, Agrawal, Sobell, & Gavin, 1999; Jardin, Larowe, Hall, & Malcolm, 2011; Yee, Serrano, Kando, & McElroy, 2019). This resulted in seven, 10-item scales. Each scale yields an aggregated index of overall obsessional and compulsive behavior related to each domain and a cut-off score of ≥8 has previously been considered the threshold for mild compulsivity (Goodman, 1989). The total score used in this analysis integrates complex composite features (*thoughts* and *behaviors*) of compulsivity (Kim, Grant, Potenza, Blanco, & Hollander, 2009; Modell, Glaser, Mountz, Schmaltz, & Cyr, 1992; Yee et al., 2019) in which to investigate the natural organization of associated affective processes. Participants could endorse multiple compulsive behaviors. In order to capture participants overall compulsive profile, we summated the total scores for each domain specific Y-BOCS.

2.3.3. Assessment of Experiential Avoidance (EA)

EA was evaluated by the Multidimensional Experiential Avoidance Questionnaire 30-item (MEAQ-30; Sahdra et al., 2016). While the Acceptance and Action Questionnaire (Bond et al., 2011) is the most widely known measure of EA, it has recently come under scrutiny for being more akin to a measure of negative emotionality than EA (Tyndall et al., 2019; Wolgast, 2014). The MEAQ assesses six dimensions of avoidance including: behavioral avoidance (α = 0.85), distress aversion (α = 0.81), distraction and suppression (α = 0.84), repression/denial (α = 0.85), procrastination (α = 0.89), and distress endurance (α = 0.86). It also yields an aggregated index of total experientially avoidant behavior (α = 0.86).

2.3.4. Assessment of psychological distress

Anxiety was evaluated by the State-Trait Anxiety Inventory Y2 (STAI-Y2), a 20-item self-report scale (α = 0.96) that examines trait (dispositional) anxiety. Participants respond on a scale ranging from 1 (almost never) to 4 (almost always). Scores range from 20 to 80, with higher scores indicative of increased anxiety.

The Perceived Stress Scale (PSS; Cohen, Kamarck, & Mermelstein, 1994) was used to evaluate the degree to which participants appraise situations in their life as stressful over the past month. It is a 10-item scale (α = 0.86), to which participants respond 0 (never) to 4 (very often). Scores range from 0 to 49 and higher scores indicate greater perceived stress.

2.4. Data analysis

Structural equation modelling (SEM) uses a combination of indicators (single variables, observed) and latent variables (underlying factors, not directly observed). SEM allows one to model multiple dependence relationships simultaneously, whilst also controlling for Type I error and measurement error. The latent variables in the model were EA, Compulsivity and Psychological Distress. Indicator variables were subscale scores on the MEAQ-30 and adapted Y-BOCS, and total scores on the STAI-Y2 and PSS.

2.4.1. Model cross-validation

A cross-validation strategy was used whereby the final model was tested and replicated in two subsamples, drawn from the same population. The sample was randomly split into two groups, calibration (n = 236) and validation (n = 233) subsamples, for cross-validation of the models using invariance testing, which tests for statistical equivalence of the model parameters across groups (Vandenberg & Lance, 2000).

2.4.2. Parameter reduction for measurement models

To conserve free parameters while also retaining the multidimensional nature of the measures (i.e. MEAQ-30 and Y-BOCS), we used the bifactor model-based index of reliability *Omega* (ω; Rodriguez, Reise, & Haviland, 2016) to reduce multiple indicators constructs to single indicator latent variables (Hayduk & Littvay, 2012). Summated MEAQ subscale and Y-BOCS domain specific scores were used as single indicators for latent variables EA and compulsivity respectively. This simplifies the measurement part of the model while still capturing the variance in each of the subscale scores attributable to the variance associated with the latent variable. Refer to Rodriguez et al. (2016) for *Omega* equations.

2.4.3. Measurement models

To reduce model complexity and potential misspecification errors, a jigsaw piece modelling strategy was used to estimate the measurement model for each component prior to combining them in the final structural regression model (Bollen, 2000). All models were tested against the null model (i.e. no association between indicator and latent variables). A two-factor model of compulsivity (i.e. latent variables being OCD-like behaviors and addiction-like behaviors) was also examined and compared against the one-factor model.

2.4.4. Model fit

Statistical analyses were undertaken using IBM SPSS 20.0, MPlus and AMOS 20.0 maximum likelihood estimation (MLE). There are currently no accepted criteria for examining model badness-of-fit using approximate fit indices (Barrett, 2007). Therefore, a combination of widely used indices were used to guide model fit decisions and are summarized in Supplementary Table S1.

3. Results

3.1. Data cleaning and preliminary analysis

Data cleaning procedures are described in Supplement. Demographic and descriptive statistics are presented in Tables 1 and 2 (Y-BOCS) and Supplementary Table S3 (MEAQ, PSS and STAI-Y2).

Table 1
Demographics of the Study Sample.

Number	469
Gender (% female)	43.7%
Age	
Mean (*SD*)	30.8 (4.9)
Range	19–48 years
Current relationship or married	56.5%
Current employment or study	
≥35 h per week	67.8%
< 35 h per week	14.9%
Studying	25.2%
Unemployed	13.0%
Income (USD)	
$0–$19,999	40.9%
$20,000–$59,000	49.9%
$60,000–$79,000	6.0%
$80,000 or more	3.2%
Highest education	
High school	13.9%
Some university (no degree)	26.0%
University with degree	60.1%
Current mental health diagnosis	17.7%
Anxiety disorder	10.4%
Depression	9.4%
OCD	0.9%
Substance-use disorder	1.0%
PTSD	1.5%
Past history of mental health diagnosis	26.9%

Correlations between indicator variables in the structural model were all significant, with coefficients ranging from 0.25 to 0.81; $p < .01$ (Supplementary Table S4).

3.2. Measurement models of EA and compulsivity

Domain specific Y-BOCS scores loaded significantly onto a single 'Compulsivity' factor. Similarly, all six-subscale scores of the MEAQ-30 formed a single 'EA' factor (Supplementary Fig. 1). Both models demonstrated acceptable fit. Factors loadings (i.e. measurement weights) were not statistically different between the groups (i.e. calibration and validation) for the Compulsivity measurement model ($\Delta\chi^2(6) = 10.23$, $p = .115$), although were different for the EA measurement model ($\Delta\chi^2(5) = 13.91$, $p = .016$). The measurement model for Psychological Distress was assessed for tau-equivalence and found to congeneric, supporting construct validity (Hair, Black, Babin, Anderson, & Tatham, 2014).

We also examined a two-factor (i.e. latent variables being OCD-like behaviors and addiction-like behaviors) model for compulsivity. Consistent with the transdiagnostic model of compulsivity, a one factor solution ($Pr_{BIC}(H_i|D) = 0.79$) was found to be a moderately better fit than the two-factor model ($Pr_{BIC}(H_i|D) = 0.21$; $\Delta BIC = 2.71$; $BF = 3.92$; Supplementary Table S5). It was also a significantly better fit than the null model, which assumes no relationship between variables ($\Delta\chi^2(5) = 253.39$, $p < .001$), further supporting a transdiagnostic conceptualization rather than diagnostically distinct behaviors. Coefficient omega was used to determine the error variance which was applied to each of the single indicator latent variables in the final model (Y-BOCS; $\omega = 0.71$, error variance = 120.49; MEAQ-30; $\omega = 0.82$, error variance = 59.68).

3.3. Mediation model: Does EA significantly and positively predict compulsivity and is this effect mediated by psychological distress?

A saturated model was specified with EA, Compulsivity, and Psychological Distress factors allowed to freely correlate, ($\chi^2(1) = 0.42$, $p = .52$; RMSEA = 0.00 [90%*CI* = 0.000, 0.149]; CFI = 0.999; SRMR = 0.005). Compulsivity was regressed onto EA and this path was statistically significant ($\beta = 0.46$, [95%*CI* = 0.36, 0.88], $p = .016$) explaining 21% of the variance. Compulsivity was then regressed onto Psychological Distress and Psychological Distress was regressed onto EA. The regression coefficient of Compulsivity on EA was no longer significant ($\gamma = 0.10$, [95%*CI* = −0.09, 0.25], $p = .33$) once Compulsivity was regressed onto Psychological Distress, indicating that the relationship between EA and Compulsivity was fully mediated by Psychological Distress (Fig. 1). The final model explained 41% of the variance in Compulsivity and 40% of the variance in Psychological Distress. Indirect effects and unstandardized coefficients are presented in Table 3.

In addition, we tested the alternative model (Psychological Distress → EA → Compulsivity), but found the path between EA and Compulsivity was not significant ($\beta = 0.10$, [95%*CI* = −0.09, 0.25], $p = .33$). The path between EA and Compulsivity was also non-significant in the latent variable moderation model (Supplementary Fig. 2; $\beta = 0.011$, [95%*CI* = −0.002, 0.025], SE = 0.007, $p = .119$). Assessment of competing models provided moderate evidence in favor of the meditation model ($Pr_{BIC}(H_i|D) = 0.78$; Fig. 1) over the moderation model ($Pr_{BIC}(H_i|D) = 0.22$; $\Delta BIC = 2.50$; $BF = 3.49$).

3.4. Cross-validation of the mediation model in the second sub-sample

The structural model (Fig. 1) was replicated using the "validation" sample data. The parameters in the model were not statistically

Table 2
Compulsive Behaviors of the Study Sample as Measured by Adapted Versions of the Y-BOCS for Each Behavioral Domain.

	Calibration sample			Validation sample		
	Mean (*SD*)	% in elevated range	Range	Mean (*SD*)	% in elevated range	Range
Gambling	1.5 (3.3)	5.9%	0–15	1.7 (3.8)	9.9%	0–16
Eating	2.7 (6.0)	17.8%	0–22	2.7 (6.2)	15%	0–24
Checking	1.8 (4.6)	11.4%	0–19	2.8 (5.9)	16.7%	0–22
Symmetry	4.4 (6.1)	26.3%	0–26	5.6 (7.0)	31.3%	0–29
Contamination	2.1 (5.2)	12.3%	0–21	2.3 (5.5)	12.9%	0–21
Shopping	1.3 (4.0)	8.5%	0–17	1.4 (4.2)	8.6%	0–18
Alcohol	2.6 (4.1)	12.7%	0–18	3.0 (4.9)	13.7%	0–21
No. of behaviors	0.95 (1.35)	–	–	1.08 (1.44)	–	–
No behaviors	–	55.5%	–	–	48.1%	–
One behavior	–	19.1%	–	–	24.9%	–
Two behaviors	–	12.7%	–	–	13.7%	–
Three behaviors	–	6.4%	–	–	7.7%	–
Four or more	–	8.0%	–	–	7.7%	–

Note. Cut-off score for determining elevated levels of symptoms is derived from a score ≥8 on the Y-BOCS. For everyday behaviors (e.g. eating, shopping, contamination), participants endorsed excessive engagement in behavior. Maximum number of behaviors endorsed by any individual was six. Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; *SD* = Standard Deviation. Min/Max Y-BOCS score for each domain = 0/40. *N* = 469.

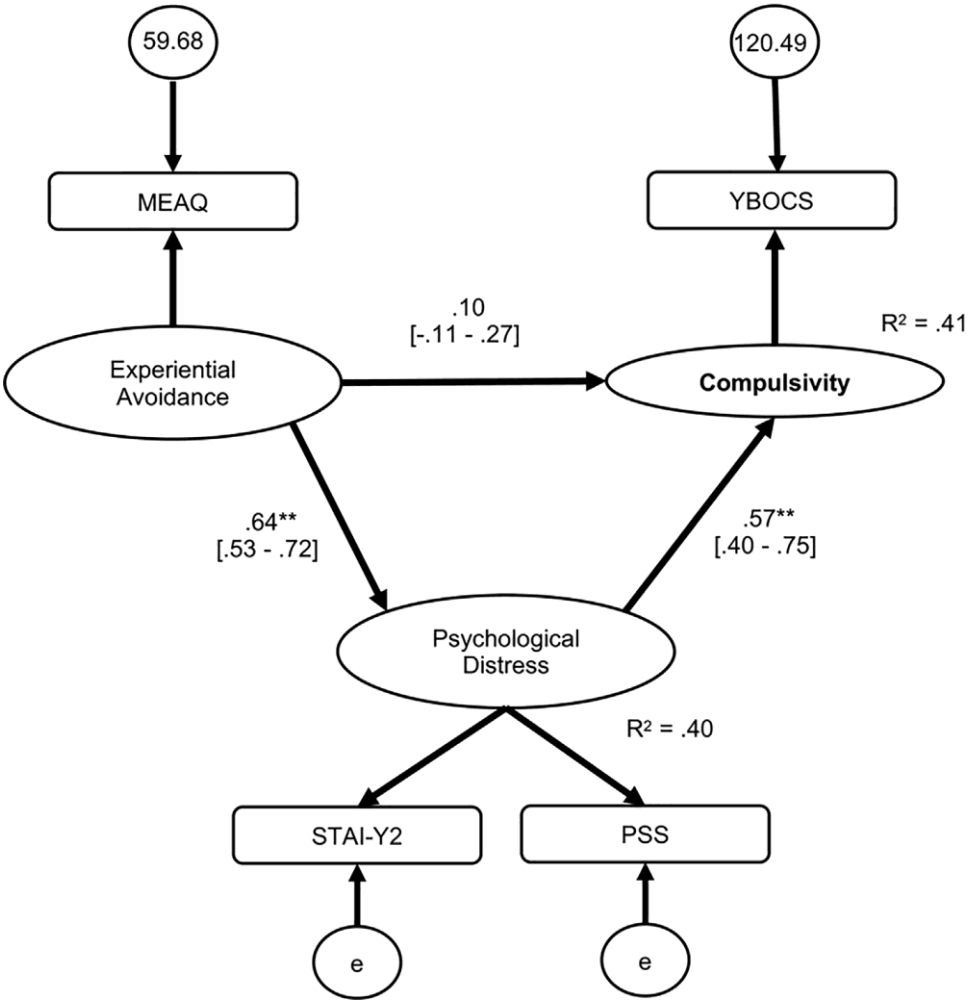

Fig. 1. Mediation model using calibration sample data. Psychological distress fully mediates the relationship between EA and Compulsivity. *Note.* Ellipses represent latent variables. Experiential Avoidance and Compulsivity are single-indicator latent variables, with loadings from the indicator fixed to reflect reliability based on coefficient omega. Single-headed arrows represent regression paths. Small circles represent error variances (i.e. variance unexplained by the model parameters). The parameter estimates displayed in the model are fully standardized and 95% *CI* represented in square brackets. Unstandardized estimates are presented in Table 3. $^{**}p < .01$, $^{*}p < .05$. $n = 236$.

Table 3
Regression Coefficients for Direct and Indirect Paths in the Mediation Model Based on the Calibration Sample.

		Unstandardized coefficients			Standardized coefficients	
		b	Std. error	95% *CI*[1]	γ/β	Sig.
Direct effects	EA → PD	0.47	0.04	0.38, 0.55	0.64	0.01
	PD → Comp.	0.80	0.14	0.58, 1.12	0.57	0.009
	EA → Comp.	0.10	0.10	−0.08, 0.29	0.10	0.33
Indirect effect	EA → Comp.	0.38	0.08	0.26, 0.58	0.37	0.004

Note. *b* = *unstandardized regression coefficient; CI* = Confidence Interval; γ/β = standardized regression coefficient from exogenous or endogenous latent variables. EA = experiential avoidance, PD = psychological distress, Comp. = compulsivity. [1] Bias corrected confidence intervals are reported for indirect effects. $n = 236$.

different between the groups on the factor loadings for Psychological Distress (i.e. measurement weights), regression weights (i.e. structural weights) and structural variances/covariances (Supplementary Table S6). However, as the factor loadings were statistically different in the measurement model for EA ($\Delta\chi^2(5) = 13.91$, $p = .016$, between samples), the model was deemed to be partially invariant at the level of the measurement weights. In the validation sample, the model and explained 28% of the variance in Compulsivity and 34% of the variance in Psychological Distress ($\chi^2(1) = 0.20$, $p = .653$; RMSEA = 0.00 [90%*CI* = 0.000, 0.134]; CFI = 0.999; SRMR = 0.005). Regression coefficients can be found in Supplementary Table S7.

4. Discussion

Addictive behaviors constitute a huge burden for individuals, their families and society. Psychiatric research is seeking to re-define the way these behaviors are conceptualized in order to gain a better understanding of the mechanisms underlying their development and maintenance. The current findings add to the growing evidence in support of *Compulsivity* as a phenotype underlying a variety of addictive behaviors characterized by intrusive thoughts, repetitive actions and functional impairment. Consistent with rates observed in our previous work (Tiego et al., 2019), we found that compulsivity was highly prevalent within the general community, with ~50% of our sample demonstrating elevated compulsive behavior in at least one domain (i.e. checking for harm, symmetry, contamination, gambling, eating, shopping and consuming alcohol). Moreover, ~30% of participants were elevated in two or more domains, suggesting that compulsivity is expressed across multiple behaviors for some individuals and emphasizing the importance of integrated treatment approaches that can address more than one problem behavior (Kelly & Daley, 2013).

There is currently no consensus in the research literature whether the compulsivity construct is comparable across OCD and addictive behaviors (Luigjes et al., 2019) and it remains highly debated whether some behaviors, such as binge-eating, should be conceptualized within models of addiction (Davis, 2017; Gordon et al., 2018). We found that a one-factor model of compulsivity was superior to the two-factor model (i.e. addictive and OCD-related behaviors). That is, individual differences were better explained by a single latent phenotype that subsumed compulsive symptoms across OCD and addiction-related dimensions, rather than two unrelated latent factors based on traditional categorical distinctions between symptom domains. Although low levels of

variance can make these factors more difficult to distinguish, this shows that compulsivity is a core feature of both OCD *and* addiction, and that it may be a specific risk factor for a variety of pathological behaviors (Chamberlain et al., 2019). The broader implication of this finding is that addiction and OCD-related problems co-occur due to common underlying phenotypes (i.e. compulsivity) and shared etiology, rather than reflecting current diagnostic categories (Chamberlain et al., 2018; Parkes et al., 2019; Tiego et al., 2019). This could help to inform more effective and individualized transdiagnostic treatment targets (Fontenelle et al., 2011; Robbins et al., 2012).

The second main aim of the study was to further understanding of the affective processes that may drive compulsive behavior, and thus addiction. In particular, we focused on the connection between EA and compulsive behavior. Several competing models were evaluated and results favored the model in which psychological distress served as a mediator between EA and compulsive behavior. In this model, EA was significantly and positively related to compulsive behaviors and psychological distress. Psychological distress was also significantly related to increased compulsive behaviors. These findings are consistent with previous findings in OCD and addiction research showing positive associations between behavior severity, EA and distress (Kingston et al., 2010; Litwin et al., 2017; Riley, 2014; Wetterneck et al., 2014).

Results showed that psychological distress fully mediated the relationship between EA and compulsive behavior, with the final model explaining 41% of the variance in compulsive behaviors and 40% of the variance in psychological distress. Thus, the extent to which EA is related to compulsive behavior is attributed to the presence of psychological distress and is consistent with the view that EA is a trait-like characteristic that influences behavior in the context of distress (Kirk et al., 2019). While this illustrates a link between poor emotion regulation capacity and the exacerbation of compulsive behavior, a notable portion of variance (~60%) remains unexplained by this model. Alternative models of compulsivity, including neurocognitive models of increased habit leaning (Gillan, Robbins, Sahakian, van den Heuvel, & van Wingen, 2015), should be considered in future research.

Although this study was cross-sectional in design, and thus unable to determine the direction of causation, results suggest individuals high on EA paradoxically experience greater levels of distress. While avoidance of emotions can help individuals to down-regulate initial discomfort, it tends to result in an overall increase in the severity and frequency of distress (Bardeen, 2015). A greater experience of distress and negative emotionality are well-established risk and maintenance factors both for OCD- and addiction-related behaviors (Adams et al., 2018; Hing, Russell, & Browne, 2017; Sinha & Jastreboff, 2013; Voltas Moreso, Hernández-Martínez, Arija Val, & Canals Sans, 2013). Compulsive behaviors may be used as a form of "self-medication" to alter or avoid negative internal experiences, which is consistent with negative reinforcement perspectives on OCD (Abramovitch & McKay, 2016) and addiction (Koob, 2015). Alternatively, given the known role of stress in promoting habitual behavior (Schwabe & Wolf, 2009), the current findings could be seen as reflecting the ability of stress to turn trait-driven behavioral tendencies, which may have been initially supported through negative reinforcement, into habitual, compulsive behaviors.

Findings highlight that EA is a potential treatment target for compulsive individuals. Despite being considered more trait-like, emerging intervention evidence has shown that EA is a modifiable treatment target (Pots, Meulenbeek, Veehof, Klungers, & Bohlmeijer, 2014; Quinlan, Deane, & Crowe, 2018). Therefore, integrating training interventions which help individuals accept and tolerate negative internal experiences hold promise as a treatment avenue for transdiagnostic compulsivity. For example, Exposure and Response Prevention trains individuals to tolerate anxiety and resist compulsions. It is widely used in OCD, however there is also emerging support for its effectiveness in other compulsive behaviors including gambling (Jimenez-Murcia et al., 2012), alcohol use (Lee, Kwon, Choi, & Yang, 2007) and video game playing (Kuczmierczyk, Walley, & Calhoun, 2010).

Finally, some limitations of this study should be acknowledged. First, the study utilized an online community-based sample, meaning it did not capture severe levels of compulsive behavior and a large portion of the sample (60%) had a university degree, which is much higher than the general population (~33%; United States Census Bureau, 2016). The transdiagnostic nature of compulsivity exhibited in this population may manifest differently in clinical samples, for example in treatment-seeking individuals. Nonetheless, such an approach did allow us to capture a broad range of behaviors, and provided insight into the levels of compulsive behavior occurring within the general-community. The second limitation is the use of a cross-sectional, correlational design which allows for cautious interpretation of results, as other alternative models could be possible (MacCallum & Austin, 2000). Cross-sectional research does not allow for inferences regarding the direction of associations between variables and thus longitudinal studies are necessary to facilitate causal evaluations (Tomarken & Waller, 2005).

5. Conclusions

The current findings highlight the prevalence of transdiagnostic compulsive behaviors within the general community, and suggest there are individuals who exhibit a profile of compulsivity across multiple behaviors. Our findings also contribute to the existing literature on affective processes associated with addictive behaviors, and provide an empirical framework for understanding the mechanisms through which EA and distress can promote transdiagnostic compulsivity. This has implications for designing psychological interventions for compulsive behavior, such as integrated treatment approaches that target more than one behavior and help individuals cope effectively with distress.

CRediT authorship contribution statement

Lauren Den Ouden: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft, Writing - review & editing. **Jeggan Tiego:** Data curation, Formal analysis, Writing - review & editing. **Rico S.C. Lee:** Conceptualization, Project administration, Writing - review & editing. **Lucy Albertella:** Project administration, Writing - review & editing. **Lisa-Marie Greenwood:** Conceptualization, Project administration, Writing - review & editing. **Leonardo Fontenelle:** Conceptualization, Writing - review & editing. **Murat Yücel:** Conceptualization, Funding acquisition, Writing - review & editing. **Rebecca Segrave:** Conceptualization, Project administration, Funding acquisition, Writing - review & editing.

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Conflict of interest and financial disclosures

Lauren Den Ouden, Rico S. C. Lee, Jeggan Tiego, Lucy Albertella, Lisa-Marie Greenwood, Leonardo Fontenelle, Murat Yücel and Rebecca Segrave declare that they have no conflict of interest.

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Appendix A. Supplementary data

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6.3. Supplementary Materials and Methods

Assessment of compulsive behaviors

Thresholding: Participants were first presented a thresholding question to determine current engagement in a behavior, evident over the past three months. For more occasional behaviors (i.e. gambling and drinking alcohol), participants were asked "*Have you gambled in the past 3 months?".* For everyday behaviors (i.e. eating, shopping), the thresholding question asked about excessive engagement in the behavior. For example, *"In the past 3 months, have you needed to eat food excessively, even though you were not hungry?".* Checking for harm behaviors included repeatedly performing routine activities to prevent harm, checking harm has not occurred to oneself or other people, and checking that nothing terrible has or will happen. For example, "*In the past three months, have you needed to repeat routine activities in order to prevent something terrible from happening?*". Symmetry behaviors included repeatedly checking a mistake has not been made, getting stuck in a cycle of re-doing activities, re-ordering and re-arranging, counting, performing routine activities to achieve balance or symmetry, and repeatedly needing to touch tap or rub things. Contamination behaviors included washing and cleaning oneself, rooms or objects to prevent contamination. If participants endorsed any of these behaviors at thresholding, they were then shown an adapted version of the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, 1989).

Assessment of compulsivity (adapted Y-BOCS): The Y-BOCS is a 10-item self-report scale. The first 5 items ask about thoughts related to a behavior (e.g. "*How much of your time was occupied by thoughts of…*") and second five items are related to the behavior itself (e.g. "*How much time did you spend on….*"). The original Y-BOCS assesses obsessions and compulsions over the past week, however we expanded this time frame to the past 3-months to capture current and persistent behavior. Individual items were also tailored to

each behavioral domain (i.e. checking for harm, symmetry, contamination, gambling, eating, shopping and consuming alcohol). For example, *"How anxious or distressed do you feel if prevented from drinking alcohol?".* This resulted in seven, 10-item scales related to each of the behaviors.

Participants responded on 5-point Likert scale. As in the original Y-BOCS, the response scale varied depending on the type of question. For example, for questions related to time occupied by thoughts or engaging in behavior, responses ranged from 0 (none) to 4 (More than 8 hours a day). While questions related to interference caused by thoughts and behaviors ranged from 0 (no interference) to 4 (complete interference). Scores on individual (domain-specific) scales could range from 0 – 40. Participants could endorse multiple compulsive behaviors. In order to capture participants overall compulsive profile, we summated the total scores for each domain specific Y-BOCS. The Y-BOCS total score could range from 0 – 280. Higher scores are indicative of greater of severity obsessions and compulsions related to a behavior and/or more pervasive obsessions and compulsions across multiple behaviors.

Table S1

Summary of indices used to evaluate model fit and competing model comparison

Fit indices	Criteria	Interpretation
χ^2	$p > .05$	The null hypothesis of 'exact fit' between the observed covariance matrix and model-reproduced covariance matrix cannot be rejected. Minimum requirement for model fit (Bollen & Long, 1993).
CFI	> .90	Higher values indicate better model fit (Kline, 2016).
SRMR	< .08	Lower values reflect closer model fit (L. Hu & Bentler, 1999).
RMSEA	< .05	Lower values reflect closer model fit (L. Hu & Bentler, 1999).
BIC	Lowest value	A goodness of fit measure, whereby lowest values are optimal (Wagenmakers, 2007)
$[Pr_{BIC}(H_i\|D)]$	Value closest to 1	Quantifies the relative probability (p ~ .00 - 1.0) that a given model provides the best fit to the observed data compared to competing models (Wagenmakers, 2007).
BF	1 – 3 = anecdotal 3 - 10 = substantial > 10 = strong	Directly compares the likelihood of two competing models in terms of a ratio (Jarosz & Wiley, 2014)

Note: χ^2 = Chi-squared statistic; CFI = Comparative Fit Index; SRMR = Standardized Root Mean Square Residual; RMSEA = Root Mean Square Error of Approximation; BIC = Bayesian Information Criterion; $[Pr_{BIC}(H_i|D)]$ = Bayesian conditional posterior probability; BF = Bates Factor.

6.4. Supplementary Results

Data cleaning and preliminary analysis: Missing data

Of the 492 individuals who completed the online questionnaire, 23 were removed for failing validation questions or incomplete responses. This brought the final sample to 469. Prior to evaluating the model, we checked raw data for normality, outliers and missing data. Univariate outliers were dealt with using winsorizing (Supplementary Table S2; Tabachnick & Fidell, 2007).

If a participant responded that they did not engage in a specific behavior (e.g. gambling, shopping, checking etc.), they were not shown the Y-BOCS for that domain. This meant that each Y-BOCS had a portion of missing data which was converted to a value of 0. The proportion of individuals who had not engaged in each behavior were as follows Y-BOCS gambling 69.5%; eating 81.7%; symmetry 45.2%; contamination 79.7%; checking 79.3%; shopping 88.5%; and alcohol 37.5%.

Table S2

Summary of the Number of Univariate Outliers that were Dealt with using Winsorizing in the Calibration and Validation Samples

	Calibration		Validation	
	Number	*Z* score range	Number	*Z* score range
Y-BOCS (gambling)	7	3.72 – 5.65	7	3.5 – 4.25
Y-BOCS (eating)	5	3.44 – 3.76	4	3.4 – 4.82
Y-BOCS (symmetry)	1	4.57	1	3.77
Y-BOCS (contamination)	6	3.44 – 5.44	7	3.30 – 3.83
Y-BOCS (checking)	8	3.31 - 4.75	4	3.45 – 3.94
Y-BOCS (shopping)	8	3.45 – 6.32	8	3.49 – 5.61
Y-BOCS (alcohol)	5	3.50 – 5.10	4	3.43 – 5.53
Y-BOCS total	3	3.47 – 3.91	3	3.42 – 4.81

Note: Calibration *n* = 236 and Validation *n* = 233. Y-BOCS = Yale-Brown Obsessive-Compulsive Scale. Y-BOCS total = summated score of all Y-BOCS domain specific scales.

Table S3

Means and standard deviations for subscales of measures of experiential avoidance (MEAQ), and psychological distress (STAI-Y2 and PSS)

	Scale range	Calibration sample Mean (*SD*)	Validation sample Mean (*SD*)
MEAQ total	30 - 180	91.8 (23.5)	95.6 (23.5)
MEAQ behavioral avoidance	5 - 30	17.1 (5.6)	17.9 (5.6)
MEAQ distress aversion	5 - 30	16.0 (5.6)	16.5 (5.9)
MEAQ distraction/suppression	5 - 30	19.2 (5.2)	19.7 (4.9)
MEAQ repression/denial	5 - 30	11.2 (5.2)	12.2 (5.8)
MEAQ procrastination	5 - 30	14.9 (6.3)	15.5 (6.3)
MEAQ distress endurance	5 - 30	21.7 (5.7)	21.2 (5.0)
STAI-Y2	20 - 80	39.2 (13.4)	40.3 (14.5)
PSS	0- 40	16.4 (7.3)	16.9 (8.4)

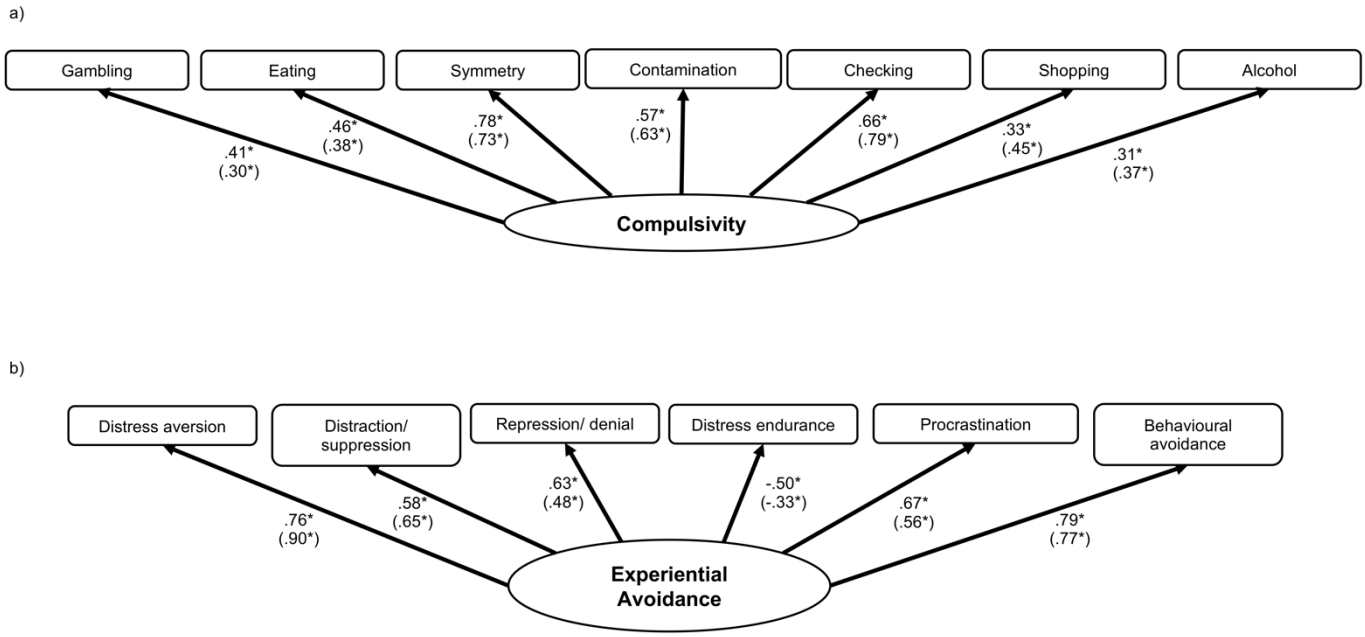
Note. MEAQ = Multidimensional Experiential Avoidance Questionnaire; STAI-Y2 = State-Trait Anxiety Inventory-Y2; PSS = Perceived Stress Scale. *SD* = Standard Deviation. Scale range represents the full range of scores possible on the respective questionnaire.

Table S4

Pearson's Product Moment Correlation Coefficients Between Each of the Indicator Variables Used in the Measurement and Structural Models

		MEAQ-30									Y-BOCS							
		BA	DA	P	DS	DE	RD	Total	PSS	STAI-Y2	G	E	Ch	Sy	Co	Sh	A	Total
MEAQ	BA		.69**	.45**	.48**	-.26**	.36**	.79**	.41**	.46**	.06	.09	.24**	.18**	.23**	.11	.08	.24**
	DA	.63**		.48**	.59**	-.29**	.43**	.84**	.45**	.48**	.14*	.18**	.25**	.26**	.24**	.17**	.19**	.34**
	P	.52**	.47**		.21**	-.53**	.52**	.66**	.55**	.53**	.09	.24**	.13*	.12	.08	.18**	.08	.22**
	DS	.44**	.49**	.13*		.01	.13*	.66**	.20**	.19**	.07	-.02	.15*	.15*	.14*	.09	.02	.14*
	DE	-.39**	-.35**	-.59**	.02		-.25**	-.15*	-.39**	-.42**	.02	-.19**	-.04	-.08	-.07	-.11	-.05	-.13*
	RD	.32**	.43**	.47**	.21**	-.36**		.66**	.37**	.35**	.26**	.15*	.19**	.08	.20**	.15*	.13*	.24**
	Total	.77**	.81**	.63**	.68**	-.22**	.62**		.49**	.49**	.18**	.15*	.27**	.20**	.24**	.18**	.13*	.31**
	PSS	.42**	.53**	.52**	.21**	-.45**	.42**	.42**		.82**	.13	.23**	.32**	.35**	.26**	.17**	.25**	.41**
	STAI-Y2	.46**	.52**	.58**	.14*	-.48**	.47**	.47**	.79**		.11	.27**	.33**	.42**	.25**	.18**	.20**	.44**
	G	.11	.15*	.19**	-.03	-.14*	.15*	.14*	.16*	.16*		.02	.21**	.18**	.28**	.19**	.21**	.39**
	E	.21**	.24**	.25**	.17**	-.19**	.18**	.26**	.35**	.38**	.06		.29**	.33**	.18**	.26**	.29**	.58**
Y-BOCS	Ch	.20**	.24**	.24**	.05	-.19**	.22**	.24**	.29**	.32**	.26**	.27**		.58**	.51**	.36**	.27**	.77**
	Sy	.22**	.29**	.23**	.07	-.18**	.26**	.27**	.41**	.48**	.37**	.40**	.49**		.45**	.30**	.30**	.78**
	Co	.16*	.20**	.18**	.13	-.10	.09	.20**	.12**	.20**	.26**	.12	.44**	.40**		.29**	.22**	.67**
	Sh	.13*	.11	.19**	.08	-.06	.18**	.19**	.18**	.22**	.06	.20**	.23**	.24**	.33**		.12	.54**
	A	.08	.09	.24**	.04	-.17*	.17*	.14*	.23**	.22**	.08	.14*	.18**	.26**	.18**	.14*		.53**
	Total	.28**	.33**	.37**	.14*	-.25**	.30**	.36**	.46**	.50**	.45**	.59**	.68**	.80**	.64**	.50**	.45**	

Note. MEAQ = Multidimensional Experiential Avoidance Questionnaire; BA = Behavioural Avoidance; DA = Distress Aversion; DS = Distraction / Suppression; RD = Repression / Denial; P = Procrastination; DE – Distress Endurance; PSS = Perceived Stress Scale; STAI-Y2 = State-Trait Anxiety Inventory-Y2; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; G = Gambling; E = Eating; Ch = Checking; Sy = Symmetry; Co = Contamination; Sh = Shopping; A = Alcohol; * significant at level .05; ** significant at level .01. Bottom half of matrix represents Calibration sample (*n* = 236)*;* Upper half of matrix represents Validation sample *(n* = 233).



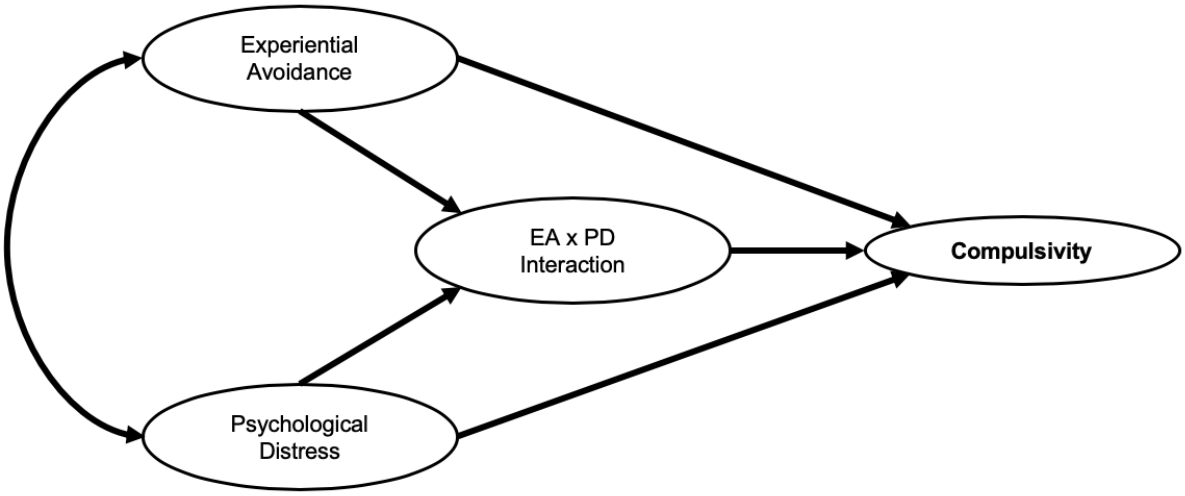
Supplementary Figure 1: Measurement model for: a) compulsivity and b) experiential avoidance for the calibration and validation samples. Parameter estimates outside parentheses represent calibration sample and inside parentheses are validation sample. *Note.* The parameter estimates are fully standardized factor loadings. Factor scaling/model identification was performed using the fixed factor method with unstandardized factor variances fixed at 1.00. Factor variances have therefore been omitted from the figure for clarity. * $p < .01$. $n = 236$ for calibration and $n = 233$ for validation.

Table S5

Competing Models Testing for Compulsivity for the Measurement Model

	χ^2	*Df*	*p*	CFI	SRMR	RMSEA (90%*CI*)	BIC	$Pr_{BIC}(H_i \mid D)$
Null	271.72	7	.000	-	-	.225 (.202 - .250)	309.96	
One Factor	18.33	12	.106	.975	.039	.047 (.000 - .088)	105.75	0.79
Two Factors	21.1	12	.050	.964	.040	.057 (.002 - .096)	108.46	0.21

Note. Calibration sample, n = 236. *df* = Degrees of Freedom; χ^2 = Chi square value for test of model fit using Full Information Maximum Likelihood estimation; *p* = significance value of the chi square test statistic; RMSEA = Root Mean Square Error of Approximation; *CI* = Confidence Interval; SRMR = Standardized Root Mean Residual; BIC = Bayesian Information Criterion; $Pr_{BIC}(H_i \mid D)$ = Bayesian conditional posterior probability



Supplementary Figure 2: Structural design of the latent variable moderation model. EA = Experiential Avoidance; PD = Psychological Distress. Ellipses represent latent variables. Single-headed arrows represent regression paths.

Table S6

Assessment for Multi-group Invariance between the Validation and Calibration Samples in the Mediation Model.

	χ^2	*df*	*p*	CFI	RMSEA (90%*CI*)	Δ*df*	$\Delta\chi^2$	*p*
Across samples (unconstrained)	.62	2	.73	.999	.00 (.000 - .065)			
Measurement weights	1.52	3	.68	.999	.00 (.000 - .060)	1	.90	.34
Structural weights	2.20	6	.90	.999	.00 (.000 - .026)	4	1.58	.81
Structural covariances	3.71	7	.81	.999	.00 (.000 - .035)	5	3.08	.69

Note. Calibration *n* = 236; Validation *n* = 233.

Table S7

Standardized and Unstandardized regression coefficients in the Mediation Model Based on the Validation Sample.

		Unstandardized coefficients			Standardized coefficients	
		b	Std. error	95% *CI*[1]	γ / β	Sig.
Direct effects	EA → PD	.42	.05	.33 - .54	.58	.008
	PD → Comp.	.72	.12	.46 - .94	.45	.009
	EA → Comp.	.13	.09	-.08 - .31	.12	.16
Indirect effect	EA → Comp.	.30	.07	.20 - .47	.26	.006

Note. b = unstandardized regression coefficient; CI = Confidence Interval; γ/ β = standardized regression coefficient from exogenous or endogenous latent variables. EA = experiential avoidance, PD = psychological distress, Comp. = compulsivity. [1] Bias corrected confidence intervals are reported for indirect effects. *n* = 233.

CHAPTER SEVEN

7. Study two: Transdiagnostic Phenotypes of Compulsive Behavior and Associations with Psychological, Cognitive and Neurobiological Affective Processing

7.1. Introductory comments

This chapter presents a research article recently submitted on June 2020 to Translational Psychiatry, entitled “Transdiagnostic Phenotypes of Compulsive Behaviour and Associations with Psychological, Cognitive and Neurobiological Affective Processing”. It is currently under review. This article is the first study to utilise a multimodal, data-driven statistical modelling approach to reclassify and identify novel, homogeneous subtypes of transdiagnostic compulsive behaviour.

A main strength of this study is the use of multiple measures, across different dimensions of function, to assess affective processing in transdiagnostic compulsive behaviour. Instead of piecemealing the data across multiple research articles, we chose to adopt an integrated approach, combining all outcome measures into a single research investigation. By integrating multiple sources of data, we can elicit multidomain profiles, which provide explanations for heterogeneity within and homogeneity between classically distinct behaviours.

Data in this study was obtained as part of a larger clinical trial investigating the impact of regular exercise and meditation on individuals with mild-moderate patterns of compulsive behaviour in the areas of eating, alcohol consumption, cleaning, checking for harm and things needing to be “just right”. As part of this trial, participant undergo a baseline and 8-week follow up assessment. The baseline data is utilised in the current research study. The advantage of focussing on a mild-moderate population is the potential to uncover “at risk” profiles and candidates for preventative interventions. Of note,

compulsive behaviour related to gambling was part of the initial inclusion criteria, however, was later removed due to difficulties recruiting this population group.

Study One (Chapter 6) established a link between psychological motivators (EA and distress) and compulsive behaviour. Study Two extends upon Study One by identifying cognitive and neurobiological affective processing systems that also influence this relationship and provides insight into how the various processing systems interact to exacerbate compulsive behaviour. The psychological motivators examined become more focussed, in that the EA sub-construct of behavioural avoidance is utilised, rather than total EA. This decision was made based on findings from Study One which showed not all sub-constructs of EA correlate with compulsivity (Chapter 6, Supplementary Table 4), suggesting they may not all be relevant. Therefore, I focussed on behavioural avoidance, as it specifically measures overt avoidance of distressing or uncomfortable situations using behaviour. In comparison to Study One, the focus also moves from broad distress (comprised in study one of anxiety and stress) specifically to stress. Stress was selected given its known role in promoting habitual behaviour.

Transdiagnostic Phenotypes of Compulsive Behavior and Associations with Psychological, Cognitive and Neurobiological Affective Processing

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ABSTRACT

Compulsivity is a poorly understood transdiagnostic construct thought to underlie multiple disorders, including obsessive-compulsive disorder, addictions, and binge eating. Our current understanding of the causes of compulsive behavior remains primarily based on investigations into specific diagnostic categories or findings relying on one or two laboratory measures to explain complex phenotypic variance. This study drew on a heterogenous sample of individuals (N = 45; 18 – 45 years; 25 female) exhibiting compulsive behavioral patterns in alcohol use, eating, cleaning, checking or symmetry. Data-driven statistical modelling of multidimensional markers was utilized to identify homogeneous subtypes that were independent of traditional clinical phenomenology. Markers were based on well-defined measures of affective processing and included psychological assessment of compulsivity, behavioral avoidance and stress, neurocognitive assessment of reward vs. punishment learning and biological assessment of the cortisol awakening response. The neurobiological validity of the subtypes was assessed using functional magnetic resonance imaging. Statistical modelling identified three stable, distinct subtypes of compulsivity and affective processing, which we labeled “Compulsive - Non-Avoidant”, “Compulsive – Reactive” and “Compulsive – Stressed”. They differed meaningfully on validation measures of mood, intolerance of uncertainty, and urgency. Most importantly, subtypes captured neurobiological variance on amygdala-based resting-state functional connectivity, suggesting they were valid representations of underlying neurobiology and highlighting the relevance of emotion-related brain networks in compulsive behavior. These data offer an integrated understanding of how different systems may interact in compulsive behavior and provide new considerations for guiding tailored intervention decisions.

INTRODUCTION

Traditional classification systems, such as the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD), remain the primary means for classifying psychopathology. However, there is mounting evidence that diagnostic categories do not capture the natural organization of psychopathology symptoms, thus impeding identification of underlying neurobiological substrates [1–5]. This has led to calls for empirically-based approaches to study psychiatric nosology that will foster neuroscientific discovery of pathogenic mechanisms across multiple levels of analysis [i.e. symptom, cognitive, neurobiological, [6–9]]. Data-driven approaches are essential in identifying psychiatric biomarkers [10,11] and the development of more effective, personalized treatments [12,13].

Data-driven clustering, a machine learning approach that learns patterns from data in the absence of group labels (e.g., disorder groups), is a promising method for reclassifying mental disorders. In psychiatry, clustering has commonly been applied to neurobiological data [5,14–17]. While such brain-based clusters may have the potential to unearth biological substrates of psychopathology [5,15,17], the variability associated with biological data risks detection of biotypes unrelated to psychiatric presentation [18]. An alternative approach is to apply clustering to so-called intermediate phenotypes [1,2,4,19–21]. Here, intermediate phenotypes are derived from behaviour and cognitive function rather than just clinical symptomatology. Critically, previous work has shown that intermediate phenotypes track variation in clinical symptoms across multiple disorders [3], and can be mapped onto underlying brain structure and function [2,19,21]. This approach has been shown to be more sensitive to detect neural correlates in psychiatric patients than conventional case-control comparisons [2,19], revealing new insights into psychopathology.

Compulsivity is an intermediate phenotype, defined by rigid, repetitive, and functionally impairing behaviors [22], that is relevant to understanding and treating a variety of mental health disorders [23]. Individual differences in *compulsivity* underlie vulnerability to disorders including obsessive-compulsive disorder (OCD), substance and behavioral addictions [2,24–26]. Compulsivity also exists outside psychiatric diagnoses, with problematic behavior frequently evident at subclinical and community-based levels [3,4]. Despite shared cognitive and neurobiological underpinnings [24,25], the causes of compulsive behaviors have traditionally been examined in the context of specific diagnostic categories [recent examples include [27–29]] or rely on one or two laboratory measures to explain phenotypic variance [30–32]. This is problematic as compulsive behavior is not constrained to one clinical category and a single outcome measure can rarely be pathognomonic for complex psychiatric behavior, with disruptions often expressed across several measures.

Our recent work has begun to address these issues, identifying compulsivity as a transdiagnostic phenotype, measurable dimensionally in both the general population and traditional diagnostic categories [1,4]. We have shown that it is closely tied to cortical-striatal-thalamic-cortical function [2]. That is, individual differences in effective connectivity across conditions such as OCD and gambling disorder are better characterized by transdiagnostic measures of compulsivity rather than comparisons based on diagnostic labels. This demonstrates that compulsivity has the potential to explain individual variance at both the symptom and neurobiological level. However, compulsivity is highly multifaceted [33,34] and our understanding of how it should be operationalized and measured remains in its infancy.

In particular, compulsivity research has tended to focus on 'cool' cognitive processes [i.e. processes that operate in affectively neutral contexts [35]] over 'hot' processes (i.e. processes that operate in motivationally and emotionally significant situations). This is despite research showing disturbances in affective processes may contribute to symptom presentation [25,28,34]. For example, biased learning of emotionally-relevant stimuli and responses may promote persistence of maladaptive behaviour in OCD [36,37] and addiction [37,38]. Therefore, we have selected a set of cognitive and affective measures tightly linked to processes relevant for compulsivity. Firstly, the Cortisol Awakening Response (CAR) is the increase in cortisol concentration within the first hour of awakening and is an indicator of hypothalamic-pituitary-adrenocortical (HPA) stress-system function [39]. Stress and hormonal stress response systems have been shown to promote habitual behavior in compulsive disorders, particularly in addiction [40–42]. Second, biases in valence-based attentional deployment underpin emotional problems in a number of mood-related clinical conditions [e.g. anxiety, depression; [43]] and are observed in substance use [37,44], problem gambling [45] and binge-eating [46,47]. Therefore, a reward versus punishment learning paradigm was used to assess attentional biases toward positive and negative stimuli [48]. Finally, psychological self-report measures of stress, experiential avoidance and compulsive behavior respectively, assessed poor perceived coping with emotional situations, disproportionate negative evaluation of aversive emotions and over-use of avoidance behaviors to manage emotions.

Evidence from animal and human studies indicate a crucial role of the amygdala in affective processing [49]. Interactions among large-scale brain-networks and the amygdala subserve many of the psychological and cognitive processes involved in affective processing [50–52]. This was illustrated in a study showing risk tolerance to be most strongly related to

amygdala-based resting-state node strength when compared to all other brain nodes [53]. Moreover, resting state functional connectivity (rs-FC) between the amygdala and medial prefrontal cortex (mPFC), a region within the emotional-appraisal network [54], made one of the greatest contributions in predicting risk tolerance. Higher rs-FC of the amygdala with mPFC (and other cortical regions) are thought to reflect capacity for greater top-down modulation [55–57], relating to less affective reactivity and compulsivity.

In this study, our broad aim was to identify naturally occurring transdiagnostic phenotypes of compulsivity, whilst including measures of affective processing that have so far received little attention. To do this, we first applied data-driven clustering to detect "hidden" subtypes based on different combinations of compulsivity and affective processing, within a sample of individuals exhibiting compulsive behavioral patterns in alcohol use, eating, cleaning, checking or symmetry. We utilized multidimensional indicators to capture affective compulsivity across psychological, cognitive and biological levels of function. Next, to assess whether the subtypes were valid representations of psychopathology, we examined the extent to which they differed on a set of validators, including self-report measures of mood and personality. Finally, to determine if subtypes reflected underlying neurobiological differences, we investigated whether they mapped onto distinct patterns of amygdala-based rs-FC.

Based on the nature of phenotypes that have emerged in other multidimensional clustering studies [19,20], we anticipated obtaining a final solution containing at least three subtypes. Namely, 1) low risk and relatively normal expression across measures of compulsivity and affective processing, 2) intermediate with evidence of mild or more localized disruptions across measures, and 3) poor outcomes across multiple measures. Subtypes were expected to exhibit outcomes consistent with these profiles on validators.

Finally, we anticipated subtypes characterized by disruptions on compulsivity and affective processing measures to exhibit reductions in amygdala-based rs-FC.

METHOD AND MATERIALS

Participants

Forty-five participants (25 females; aged 18-46 years) reporting current and persistent engagement in either an OCD- or addiction-related compulsive behavior were enrolled in the study. Participants were part of a larger behavioral intervention trial targeting mild to moderate compulsive behaviors. Data used in the current study is from the baseline assessment, prior to any intervention. Compulsive behavior was defined as a score ≥ 5 on the compulsive subscale of the self-report Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; modified for alcohol and eating) over the past 3-months. A subscale score of ≥ 5 is indicative of mild OCD [58] without necessarily meeting diagnostic threshold for the disorder. Participants were excluded for lifetime and current psychological, neurological and medical conditions that could affect testing procedures (full inclusion and exclusion criteria detailed in Supplementary Material). All experiments were performed in accordance with relevant guidelines and regulations of Monash University Human Research Ethics (Project ID: 0437).

Materials

Additional detail on the materials, MRI data acquisition and pre-processing can be found in Supplementary Material.

Compulsive behavior. Originally developed for OCD, the Y-BOCS has been adapted to measure addiction-related compulsive behaviors [59,60]. Adapted versions used in this study measure self-reported obsessions and compulsions over the past three-months related to either *checking, achieving symmetry, cleaning, alcohol consumption or eating*. Where participants endorsed multiple behaviors, the Y-BOCS with the highest score was used in the analysis. While the inclusion criteria of ≥ 5 on the compulsive subscale of the

YBOCS was used to ensure the data captured self-reported compulsive phenotypes associated with the repetitively performed behaviours, the total score used in the analysis integrates complex composite features (*thoughts* and *behaviors*) of compulsivity [61–64] in order to investigate the natural organization of associated psychological, cognitive and neurobiological processes. Y-BOCS total scores can be interpreted as subclinical (0-7), mild (8-15), moderate (16-23), severe (24-31) and extreme (32-40).

Behavioral Avoidance. The tendency to use behaviors to reduce or avoid negative mood states was assessed using the behavioral avoidance subscale of the Multidimensional Experiential Avoidance Questionnaire 62-item [MEAQ-62; [65]]. This subscale measures overt avoidance of distressing or uncomfortable situations, whereby higher scores index increased use of behavioral strategies to avoid negative internal experiences. Normative data shows community-based adults score M = 34.40, SD = 10.41, while psychiatric patients score M = 42.36, SD = 11.13.

Stress. The Perceived Stress Scale [PSS; [66]] assessed the degree to which participants felt they could cope and respond to stressors. Higher scores reflect increased distress while lower scores reflect good coping or fewer stressors/challenges present. Normative data from community-based adults aged 18-29 years elicited M = 14.2, SD = 6.2.

Valence Learning Bias. A computerized assessment called “BeanFest” served as our neurocognitive measure of reward vs. punishment learning biases [48]. The task measures individual differences in learning based on wins and losses. Participants attempt to win points and avoid losses by learning which beans are rewarding (win) and punishing (loss). After the learning phase, participants classify beans as “helpful” or “harmful” to assess learning of rewarding vs punishing beans (i.e. valence learning bias). Valence learning bias is calculated as the difference between the proportion of rewarding and punishing beans

classified correctly. Scores can range from – 1.00 to 1.00, whereby scores below zero indicate punishment learning bias and scores above zero indicate reward learning bias.

Cortisol Awakening Response. Participants collected three saliva samples per day over two consecutive working days (awakening (t_0), 30-minutes (t_{30}) and 45-minutes after awakening (t_{45})). To quantify the cortisol awakening response (CAR), the CAR salience index (difference between mean secretion rate before and after 30-mins: Formulaic expression: $((t_{30} – t_0)/30) – ((t_{45} – t_{30})/15)$) was used as it was recently shown to perform significantly better than traditional CAR calculations at revealing more trait-like individual differences [67].

MRI data acquisition and pre-processing.

Acquisition: The dataset was acquired on a Siemens MAGNETOM Skyra 3T scanner. T1-weighted (T1w) images are TE = 2.55 ms, TR = 1.52 s, flip angle = 9°, 208 slices with 1 mm isotropic voxels. EPI images for resting-state fMRI (rs-fMRI) are TE = 30 ms, TR = 2.5 s, flip angle = 90°, 189 volumes, 44 slices. Participants were asked to look at a fixation cross on the screen, and not fall asleep.

Pre-processing: T1w and rs-fMRI images were pre-processed using fmriprep (version 1.1.1) on a CENTOS 7 cluster computing system (www.massive.org.au), including: distortion correction, head motion correction, slice timing, special normalization to standard space [i.e., Montreal Neurological Institute (MNI) space], confound signals removal using ICA-AROMA and CompCor and smoothing with 6mm gaussian kernal. The rs-fMRI images were de-trended and band-pass filtered at 0.01-0.1Hz. The rs-fMRI images were used as input to calculate amygdala-based functional connectivity network. Bilateral Amygdala seeds were generated from Harvard-Oxford subcortical template using FSL. The probability template is threshold at 90% and saved as the seed of a binary mask. Functional connectivity (FC) maps

were generated using RESTplus V1.22 [68]. Further voxel-based statistical analysis on FC maps are detailed in Statistical Analyses section.

Procedure

With the exception of saliva samples, all data collection was conducted at Monash University BrainPark, Melbourne. Participants completed two 90-minute research sessions which were conducted within one week of each other. Session one involved consent, diagnostic interview and questionnaires. Session two comprised the MRI brain scan and cognitive assessment. Saliva sampling protocol was completed at the participants' homes using a home testing kit (SalivaBio) within one week of completing session two. See Supplementary Materials for detail on saliva collection, storage and analysis.

Statistical Analyses

Identifying clusters. We clustered individuals using measures of compulsivity (Y-BOCS), behavioral avoidance (MEAQ), stress (PSS), valence learning bias (BeanFest) and CAR (MnInc). Each variable was *Z*-scored so that it contributed equally to the distance measure. A combination of hierarchical and k-means cluster analyses (performed in IMB SPSS Statistics 25) was used to detect distinct subtypes. A hierarchical agglomerative method (Ward's method) with squared Euclidean distance was first implemented to explore the number of clusters for entry into k-means analysis. The number of clusters was decided following examination of the dendrogram, and by identifying large differences between consecutive numbers in the agglomeration schedule [69]. Although a two-cluster solution is almost always supported at the hierarchical clustering stage [69], it offers limited value in eliciting meaningful profiles across multiple dimensions and was therefore not considered further.

Stability of the final solution was confirmed through several assessments. First, the agreement between the two method solutions (i.e. Ward's method and k-means) was assessed using Cramer's V test. Next, the final solution (derived from the k-means analysis) was further assessed by running 10 passes with different random seed starting points [70] and comparing results by Cohen's kappa (*k*) and intraclass correlation coefficient (ICC). Overall, a $k < 0.2$ reflected poor agreement; 0.21 - 0.4, fair; 0.4 - 0.6, moderate; 0.61- 0.8, good; and $k > 0.81$, very good. Finally, stability of the cluster solution was tested using a bootstrap technique. Using the R package "fpc" version 2.1.9, the Jaccard coefficient was calculated to compute the structural similarity (ranging from 0 to 1) of 2000 resampled clusters with those derived from the original data [71]. Valid, stable clusters should yield Jaccard coefficients $\geq .75$ and values above .85 are considered "highly stable". Discriminant function analysis (DFA) was run with cluster input variables as predictors and cluster membership as criterion variables to examine the cluster solutions' classification accuracies and inspect the separation of the clusters in discriminant function space.

Cluster differences on validating measures. The validity of the optimal solution was assessed against self-report measures including intolerance of uncertainty (IUC), urgency, anxiety and depression, as well as demographic and clinical characteristics. MANOVAs, ANCOVAs and chi-squared analyses were used where appropriate, with Bonferroni adjustment for multiple comparisons on post-hoc analyses. Amygdala-based FC maps for each subtype were generated using one sample *t*-test to visually compare the network pattern (SPM12 software). An F-contrast was used to examine the subgroup effect on the amygdala-based rs-fMRI network, controlling for age and sex. Then, independent t-tests were conducted to examine directional differences between each subtype. For each comparison, results were first thresholded at $p_{uncorrected} < .001$ with cluster size > 10, then

corrected for multiple comparisons error at the cluster level of $p < .05$, using family wise error (FWE) correction. Further detail on statistical analysis in Supplementary Methods.

RESULTS

Sample size

There is no generally accepted minimum sample size in clustering, however a sample size of at least 2^m, where *m* equals the number of clustering variables has been recommended [72]. The minimum sample size for the current investigation is $2^5 = 32$.

Descriptive analyses

Primary compulsions included checking (*n* = 5), achieving symmetry (*n* = 13), cleaning (*n* = 9), alcohol consumption (*n* = 6) or eating (*n* = 12). 22 participants met diagnostic criteria for current OCD (*n* = 12), binge-eating disorder (*n* = 4) and alcohol-use disorder (*n* = 6). Variable means and standard deviations, missing data, outliers and assessments of normality and multicollinearity are detailed in Supplementary Results. Pearson's correlations between variables ranged from .02 to .52.

Hierarchical cluster analysis

Cluster analysis based on Ward's method provided greatest support for two- and three-cluster solutions. The dendrogram supported up to four potentially occurring clusters (Supplementary Figure S1). However, percentage change in the agglomeration coefficient argued against a four-cluster solution, as the increase exceeded that of the previous stage [Supplementary Table S3; [69]]. The largest change was seen in the two-cluster solution (35.50%), followed by the three-cluster solution (20.58%). Given a three-cluster solution has the potential to offer more meaningful profiles across multiple dimensions, the three-cluster solution was carried into further analyses.

K-Means cluster analysis

K-mean cluster analysis was next implemented, specifying a three-cluster solution. There was excellent agreement between Ward's method and K-means clustering, with

Cramer's V = .86 and Cohen's kappa = .83, both $p < .001$. The three-cluster solution showed excellent stability when the seed starting point was randomly altered 10 times. There was high profile similarity (ICC > .90) between all solutions and they all demonstrated very good to excellent agreement with the original solution (k = .70 – 1.00). Average Jaccard bootstrap values for clusters were .77, .80 and .96, indicating the clusters were valid and stable. DFA indicated the three subtypes were adequately separated in discriminant function space (Supplementary Figure S2) and that 100% of cases were correctly classified.

Subtype characteristics

Subtype profiles (Figure 1) reflected the following:

1. **Compulsive - Non-Avoidant (CNA; n = 14):** mild-moderate compulsivity, low behavioral avoidance and mild stress (or good perceived ability to cope with life stressors); low CAR; negative learning bias.
2. **Compulsive - Reactive (CR; n = 18):** mild-moderate compulsivity, mildly elevated behavioral avoidance and mild stress (or good ability perceived to cope with life stressors); high CAR; strong positive learning bias.
3. **Compulsive - Stressed (CS; n = 13):** moderate-severe compulsivity, highly elevated behavioral avoidance and very high stress (or poor perceived ability to cope with life stressors); moderate CAR; positive learning bias.

Subtype differences were assessed on demographic and input variables (Table 1), as well as on validators (i.e. IUC, urgency, anxiety and depression; Table 1 and Supplementary Figures S3, S4 and S5). Results of MANOVAs, ANOVAs and Chi-squared tests are detailed in Supplementary Results.

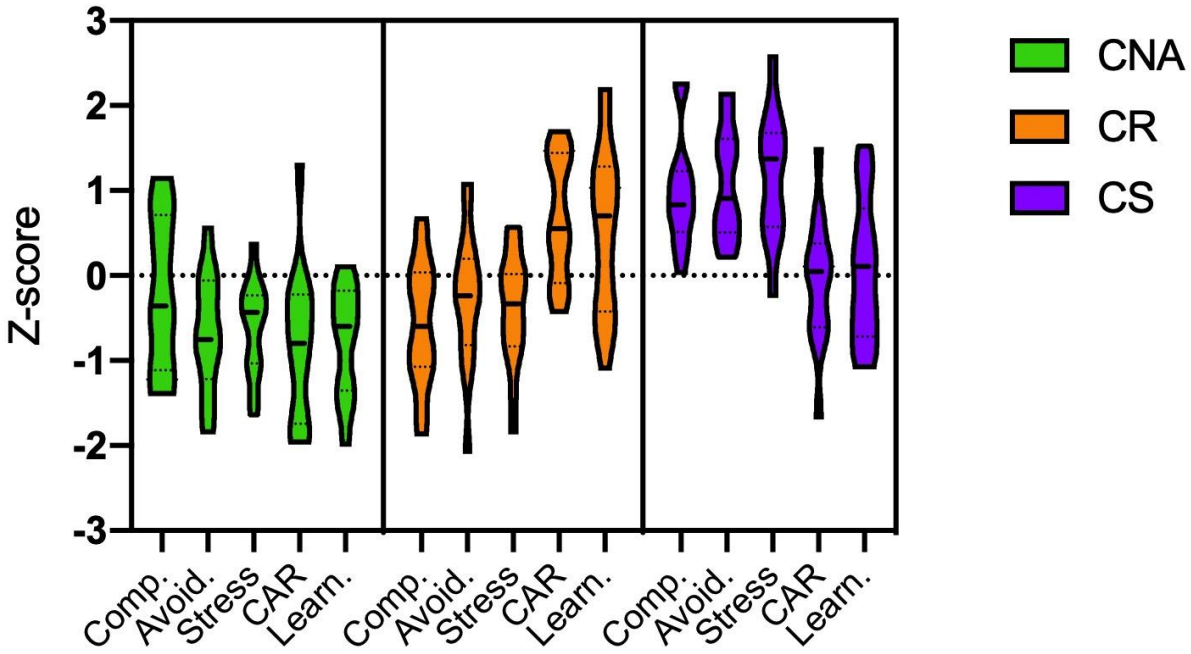

Fig. 1 Violin plots for each of the variables by subtype. Comp. = Y-BOCS z-score for participant's primary compulsion; Avoid. = MEAQ behavioral avoidance z-score; Stress = PSS z-score; CAR = cortisol awakening response salience z-score; Learn. = valence learning bias z-score as measured by the BeanFest task. CNA = Compulsive Non-Avoidant; CR = Compulsive Reactive; CS = Compulsive Stressed subtype.

Differences in amygdala-based rs-FC between subtypes

Subtypes showed no differences in framewise displacement (Table 1), indicating rs-FC findings were not due to motion artefact. Whole-brain analysis of amygdala-based rs-FC revealed connectivity patterns largely consistent with previous studies [73,74] and showed functional coupling between the amygdala and regions within affect processing networks [54]. Figure 2 illustrates the whole-brain resting-state functional connectivity map for bilateral amygdala seed for the three subtypes at the same threshold (T = 7.7, p = $1e^{-09}$). The CNA subtype demonstrated the greatest, widespread functional synchronicity between the amygdala and other brain regions, while the CS group exhibited the least brain regions functionally synchronized with the amygdala. The CR subtype demonstrated a functional

connectivity pattern more widespread than the CS subtype, albeit more constrained than the CNA subtype.

Further statistical group comparisons revealed the CR subtype exhibited significantly decreased functional connectivity of the amygdala at the left superior parietal lobe when compared to the CNA subtype (Table 2; Figure 3a). The CS subtype demonstrated decreased amygdala functional connectivity at several regions compared to the CNA subtype (Figure 3b. These included multiple regions within the frontal and temporal lobes, the insula, cerebellum, cuneus, precuneus, superior parietal lobe and middle occipital gyrus, as well as subcortical regions, including the thalamus, putamen, pallidum, caudate and nucleus accumbens. No significant differences were observed between the CR and CS subtypes.

Table 1.

Demographic and subtype profiles for main input and validating variables

Subtype	1 (*n* = 14)	2 (*n* = 18)	3 (*n* = 13)		
	CNA	CR	CS	Post hoc comparisons ($p < .05$)	Effect size (η_p^2)
	M (SD)	*M (SD)*	*M (SD)*		
Age	24.57 (4.86)	24.56 (4.90)	26.31 (7.77)	$p = .52$	
Sex (m/f)	7/7	11/7	2/11	$p = .036$	
Primary compulsion (Add/OC)	8/6	6/12	4/9	$p = .67$	
FD	.11 (.053)	.11 (.065)	.085 (.028)	$p = .47$	
Measures used in cluster formation					
Y-BOCS Total	15.57 (5.60)	13.22 (4.62)	23.00 (4.20)	1 < 3; 2 < 3	.38
Behavioral Avoidance (MEAQ-BA)	30.36 (6.69)	37.78 (6.67)	46.77 (9.44)	1 < 2; 1 < 3; 2 < 3	.42
Coping with stress (PSS)	18.14 (2.80)	19.28 (3.29)	27.00 (3.79)	1 < 3; 2 < 3	.55
CAR salience	.027 (.22)	.394 (.18)	.210 (.19)	1 < 2	.39
Valence learning bias	- .093 (.15)	.213 (.23)	.100 (.20)	1 < 2; 1 < 3	.30
Validation measures					
Anxiety (STAI-Y2)	40.29 (6.07)	42.83 (6.65)	49.69 (6.40)	1 < 3; 2 < 3	.25
Depression (CESD-R)	8.93 (6.93)	7.22 (4.61)	23.23 (12.04)	1 < 3; 2 < 3	.39
Intolerance of uncertainty (IUS)	25.00 (5.38)	32.28 (6.28)	40.31 (9.87)	1 < 2; 1 < 3; 2 < 3	.51
Positive urgency (UPPS-P)	23.21 (6.87)	31.50 (6.00)	33.08 (6.21)	1 < 2; 1 < 3	.32
Negative urgency (UPPS-P)	24.57 (6.21)	25.94 (3.84)	31.62 (3.89)	1 < 3; 2 < 3	.25

Note: CNA = Compulsive – Non-Avoidant; CR = Compulsive – Reactive; CS = Compulsive – Stressed; Add. = addiction-related (eating and alcohol) compulsivity; OC = obsessive compulsive; FD = Framewise displacement; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; MEAQ-BA = Multidimensional Experiential Avoidance Questionnaire Behavioral Avoidance subscale; PSS = Perceived Stress Scale; CAR salience = cortisol awakening response salience score, measured in nanomoles per liter(nmol/L); STAI-Y2 = State-Trait Anxiety Inventory Y2; CESD = Centre for Epidemiologic Studies Depression Scale Revised; IUS = Intolerance of Uncertainty Scale; UPPS = UPPS-P Impulsive Behavior Scale; η_p^2 = partial eta squared

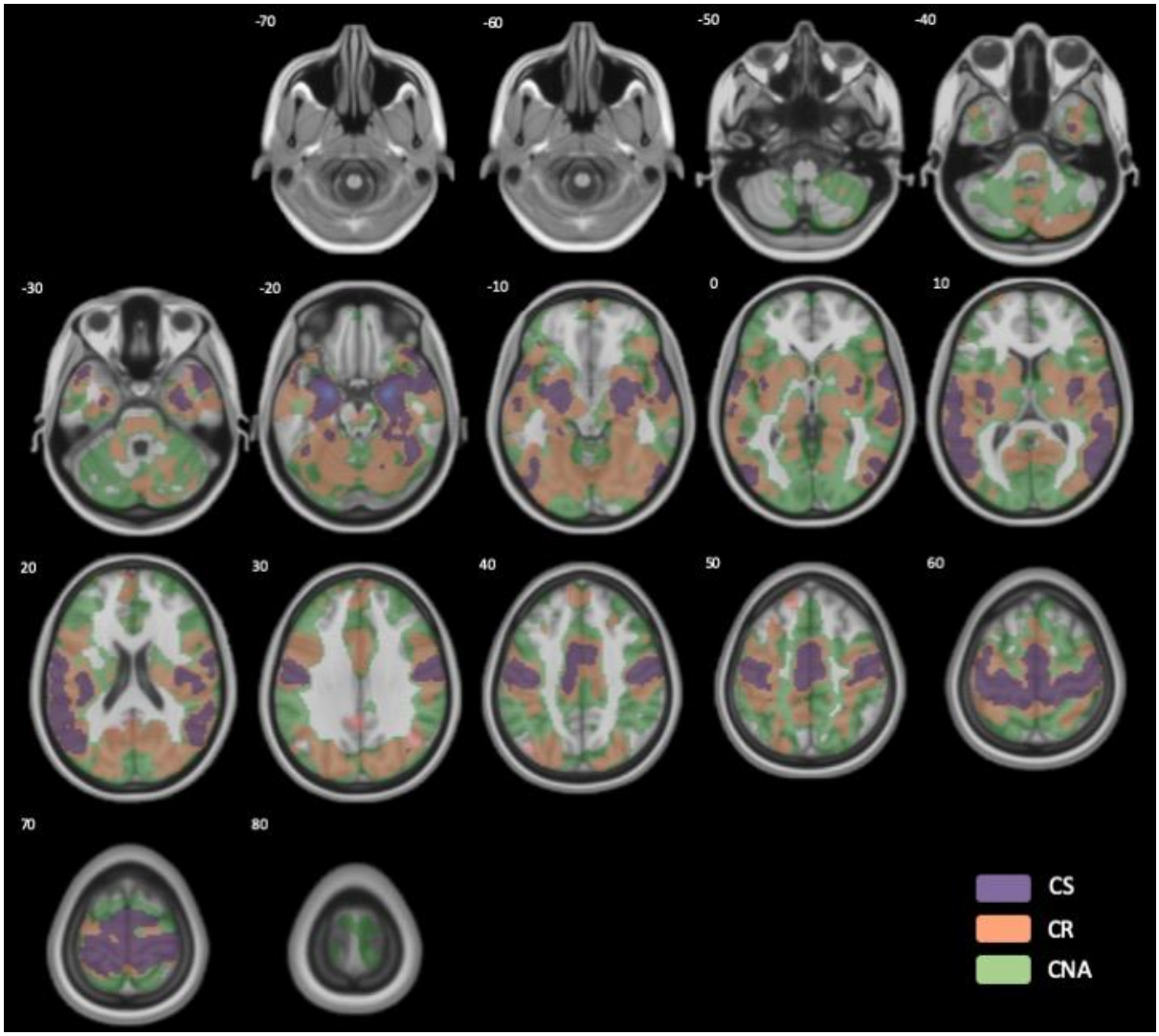

Fig. 2. Whole-brain resting-state functional connectivity map for bilateral amygdala seed for three subtypes (threshold used $T = 7.7$, $p = 1e^{-09}$): Colors represent brain regions showing functional correlation with amygdala function at rest. CNA = Compulsive Non-Avoidant; CR = Compulsive Reactive; CS = Compulsive Stressed subtype.

Table 2.

Brain regions exhibiting a significant difference between subtypes in the resting-state functional connectivity of the bilateral amygdala ($p < .001$)

P_{FWE}	K	Peak t	MNI coordinates			Hem.	Region
			x	y	z		
CNA > CR							
.018	545	5.1	-24	-44	60	L	Superior Parietal Lobe
CNA > CS							
< .001	22,189	6.18	1	-78	-18	R	Cerebellum
		5.74	-30	-80	-22	L	Cerebellum
		4.81	9	-97	4	R	Cuneus
		5.52	-7	-102	-6	L	Cuneus
		4.09	25	-81	-13	R	Middle Occipital Gyrus
		4.88	-27	-80	-15	L	Middle Occipital Gyrus
< .001	2,857	4.71	24	-60	52	R	Precuneus
		4.25	-3	-46	55	L	Precuneus
		4.67	25	-62	53	R	Superior Parietal Lobe
		4.04	-25	-62	53	L	Superior Parietal Lobe
		4.37	-4	-46	58	L	Paracentral lobule
		4.46	22	-24	8	R	Thalamus
		3.79	26	-10	7	R	Putamen
		3.54	23	-10	2	R	Pallidum
< .001	2,203	4.57	52	18	4	R	Inferior Frontal Gyrus
		4.46	62	6	-2	R	Superior Temporal Gyrus
		4.00	34	2	-1	R	Insula
		4.41	10	12	4	R	Caudate
.001	1,080	4.35	-20	-4	6	L	Pallidum
		4.27	-10	14	-2	L	Caudate
		3.79	-15	-22	15	L	Thalamus
		3.71	-25	-1	-3	L	Putamen
		3.91	-12	12	-7	L	Nucleus Accumbens
.001	1,014	4.81	2	18	38	R	Middle Cingulate gyrus
		3.90	0	18	56	Mid	Superior motor area
		4.05	-2	21	54	L	Superior Frontal Gyrus

.002	929	5.47	32	54	32	R	Superior Frontal Gyrus
		4.77	34	64	14	R	Middle Frontal Gyrus
.006	709	4.51	-38	20	-8	L	Inferior frontal Gyrus
		4.19	-50	12	8	L	Precentral Gyrus
		3.93	-38	16	-8	L	Insular
.034	452	4.21	-40	44	32	L	Middle Frontal Gyrus

MNI, Montreal Neurological Institute; P_{FWE}, p value after family-wise error correction; k, cluster size; Hem., Hemisphere; L, Left hemisphere; R, Right hemisphere; Mid., Midline. CNA = Compulsive Non-Avoidant; CR = Compulsive Reactive; CS = Compulsive Stressed subtype.

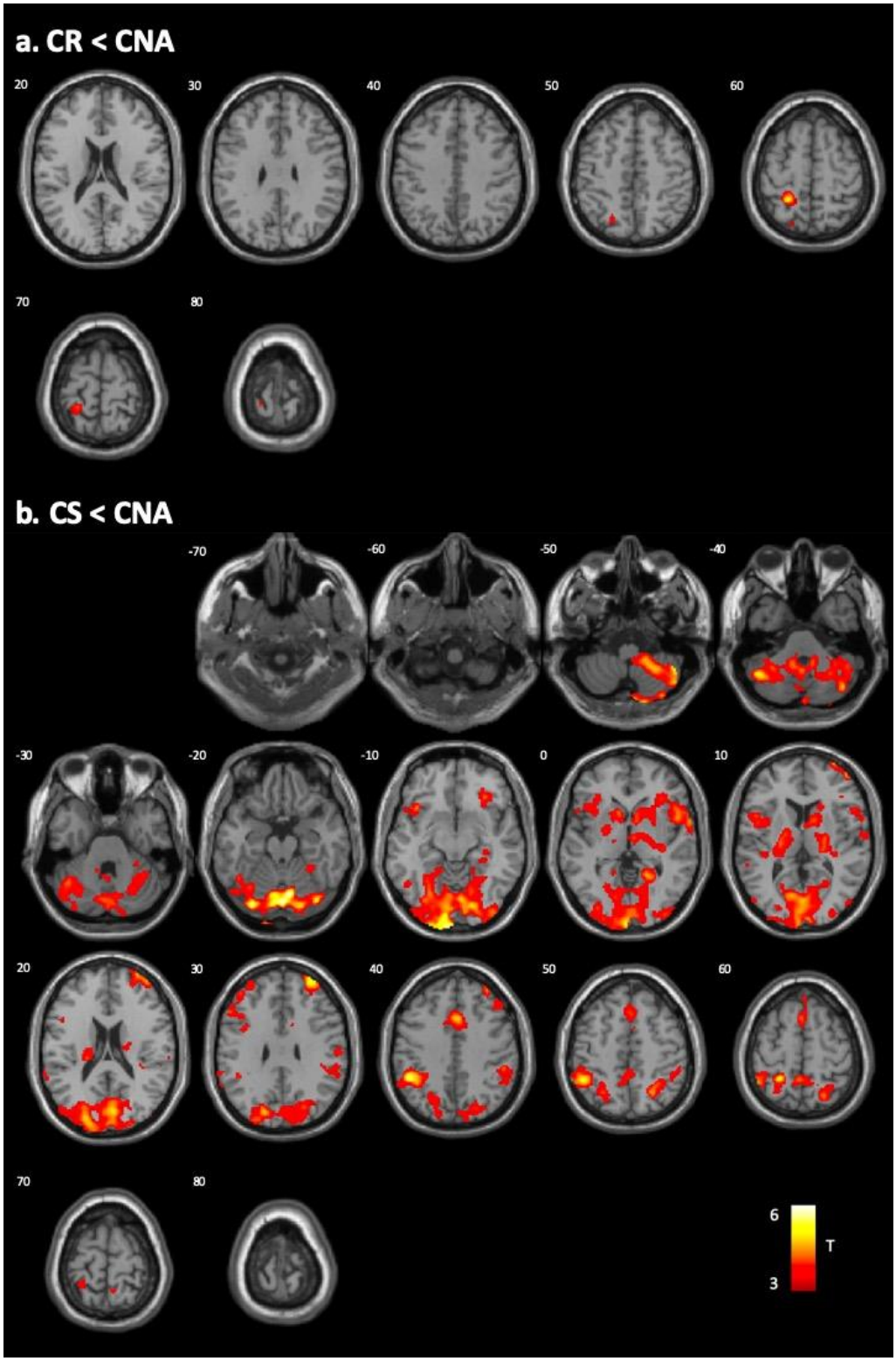

Fig. 3. Brain regions showing reduced amygdala-based resting-state functional connectivity in a) the CR (Compulsive Reactive) subtype compared to the CNA (Compulsive Non-Avoidant) subtype, and b) CS (Compulsive Stressed) subtype compared to the CNA subtype Colored areas indicate significant regions after family-wise correction at cluster level (P_{FWE} < .05).

DISCUSSION

A multimodal, data-driven statistical modelling approach was used to identify novel, homogeneous subtypes of transdiagnostic compulsive behavior. Comprising a range of traditional labels (i.e. cleaning, checking, symmetry, compulsive eating and alcohol use), subtypes identified independent of behavioral domain and were instead based on the current understanding of shared affective processes underpinning compulsivity. Each subtype included all types of behavior demonstrating transdiagnostic expression, and exhibited unique profiles across psychological, cognitive and neurobiological indicators. Meaningful differences were observed on validating measures of depression, anxiety, intolerance of uncertainty and urgency. Most importantly, subtypes mapped onto amygdala-based brain network connectivity, illustrating their ability to capture neurobiological distinctiveness and highlighting the relevance of emotion-related brain networks in compulsive behavior.

An important feature of our approach, and other investigations reclassifying mental disorders [17,19,20], was the integration of multidimensional indicators to form intermediate phenotypes. This approach can reveal “hidden” subtypes, which demonstrate unique profiles of impairment on indicator variables. Consistent with similar studies in affective and psychotic disorders, multiple subtypes emerged (i.e. CNA, CR and CS) that exhibited different combinations of impairment on measures of compulsive-emotionality. Subtypes with poorer outcomes exhibited greater reductions on amygdala-based rs-FC.

Subtype CS was most impaired, characterized by moderate-severe compulsivity, over-use of maladaptive emotion regulation strategies (i.e. avoidance) and poor perceived ability to manage stress. Widespread reductions in functional connectivity between the amygdala and nodes within the visual attention network, salience network, DMN and limbic

network were also evident, as was decreased connectivity between the amygdala and cerebellum. The cerebellum is intrinsically connected to the amygdala [75] and is considered a reliable biomarker of emotional states [76] and affective processing [77]. Subtype CNA exhibited mild-moderate levels of compulsive behavior and relatively low/neutral levels across all other indicators, suggesting no obvious emotional processing disruptions. Neurobiologically, there was no evidence of functional connectivity reductions in amygdala linked networks. Subtype CR also demonstrated mild-moderate levels of compulsive behavior, however demonstrated evidence of emotion processing disruptions on other indicators. Subtype CR was characterized by an attentional bias for rewarding stimuli, elevated CAR and mildly elevated tendency to avoid negative emotions. Reductions in amygdala rs-FC were observed, albeit less pronounced and more localized compared to subtype CS. Reductions were primarily in regions encompassing main nodes of the visual attention and DMN.

The initial classification of compulsivity (i.e. YBOCS compulsive subscale score ≥ 5) seems to produce a robust amygdala linked brain network, within which there is further phenotypic variance. There was remarkable consistency between amygdala-based FC reductions and the degree of subtype impairment (Figure 2). This emphasizes the importance of the amygdala and its network connectivity in explaining individual variance in compulsive behavior. Widespread decreases in rs-FC between limbic regions (amygdala, hippocampus) and other brain networks including basal ganglia, default mode and attention networks have been found in OCD [78], anxiety, and depression [55,79]. Decreased functional coupling between the amygdala and cortical/subcortical regions may represent a neural mechanism for increased vulnerability for emotion driven psychopathology [80–82].

Aspects of the subtype profiles are consistent with past literature and, taken as a whole, reveal processes which may lead to compulsive behavior. The most severe symptom presentation in subtype CS is consistent with previous findings linking elevated stress to increased pathological repetitive behavior in addictions [42,83,84] and OCD [85]. Stress promotes habitual behavior [86] and stress hormones (e.g. cortisol) have been argued to reduce goal-directed control over behavior while increasing connectivity between the amygdala and dorsal striatum [region implicated in habit learning and action initiation [87–89]]. The co-occurrence of stress and elevated symptom severity in subtype CS could reflect the ability of stress to turn trait-driven behavioral tendencies into habitual, compulsive behaviors.

Despite reporting the greatest level of stress, subtype CS exhibited only a moderately elevated CAR relative to other subtypes. The relationship between stress and the CAR may present in an inverted-U shaped manner, whereby the CAR is greater under conditions where people actively cope with stressors, while in more severely stressful conditions where coping is reduced, a decrease in the CAR starts to occur [39,90,91]. This likely reflects cortisol levels increasing with symptom associations until a threshold is reached and the HPA-axis is down-regulated [92].

By comparison, subtype CR exhibited an elevated CAR coupled with low self-reported stress. The combination of an elevated CAR and low self-reported distress response to stress could be seen as reflecting the link between increased CAR and biological preparedness to actively manage stressors [93]. CR subtype was further differentiated by a strong propensity towards visual reward learning. Reward learning biases on the same task have been linked to increased impulsivity [94], a construct thought to overlap and increase the risk for compulsivity [1]. This finding was validated on self-report measures, which

showed this subtype experienced elevated urgency toward positive stimuli/emotions. Increased reward learning, coupled with behavioral avoidance tendencies (i.e. use of behaviors to avoid uncomfortable emotions) and a biological stress-related undertone, may interact to increase vulnerability (albeit mildly) to compulsive behavior. This interpretation is supported neurobiologically by amygdala functional connectivity disruptions between regions within the visual attention and DMN, responsible for visual perception of stimuli which elicit emotional responses and appraisal of emotional stimuli [54].

Subtype CNA appeared most analogous to a healthy group. They demonstrated low self-reported stress and avoidance behaviors and a weak punishment learning bias on the learning task, a finding common within the general population [48]. The low CAR coupled with low stress, suggests minimal daily life stressors. Given the absence of functional disruptions on amygdala-based brain imaging, emotion processing disruptions may not contribute to compulsive behavior in this subtype. Behavior may be better explained by contributory factors not examined here or represent normal human function.

The clinical utility of subtypes ultimately rests on their ability to inspire new research avenues and guide precise treatment recommendations. Treatments for subtype CS could focus on developing adaptive emotion regulation strategies and improving tolerance for negative emotions. Improvements may be visible on amygdala resting-state endpoints. In light of the CR profile, cognitive recalibration of reward/approach attentional biases [95] offers a therapeutic avenue. This subtype presents a target for preventative interventions and investigating risk predictions. Given the elevated CAR and emerging avoidance tendencies, they may be at risk for progression of pathological behavior. This is further supported by emerging disruptions in amygdala network connectivity. Finally, subtype CNA

encourages examination of alterative models for classifying compulsive behavior, including reward-based models involving the ventral striatum and related neural networks [25,96].

This study represents the first of its kind in the area of compulsivity. Results demonstrate the promise of this approach in generating new understandings of compulsive behavior. Although there are limitations associated with clustering methods [97], precautions were taken to assess the validity of subtypes. Meaningful differences on amygdala rs-FC indicate subtypes were valid representations of underlying neurobiological variance. Future studies with larger sample sizes may compliment this approach with other validation techniques (e.g. split sample and replication) or run alternative clustering methods [98]. A larger sample size may allow for additional clusters/subtypes in the data to be uncovered [99]. For convenience, and in line with previous studies [64], compulsivity was quantified using total YBOCS scores across disorders, which incorporates obsessions and compulsions (both of which are highly correlated and intrinsically linked [100,101]). Nonetheless, future work could consider other conceptualizations of compulsivity. Finally, our analyses utilized a general community sample with mild to moderate levels of compulsive behavior and did not capture more severe clinical presentations. Subtype profiles and brain network connectivity disruptions may manifest differently in clinical samples. Longitudinal investigations could clarify how subtypes and their neural substrates evolve overtime, from mild/moderate manifestations to severe compulsive behavior.

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DISCLOSURES

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CONTRIBUTIONS

Lauren Den Ouden: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft, Writing - review & editing. **Chao Suo:** Conceptualization, Data curation, Formal analysis, Project administration, Writing - review & editing. **Lucy Albertella:** Conceptualization, Data curation, Project administration, Writing - review & editing. **Lisa-Marie Greenwood:** Conceptualization, Data curation, Project administration, Writing - review & editing. **Rico Lee:** Conceptualization, Formal analysis, Writing - review & editing. **Leonardo Fontenelle:** Conceptualization, Writing - review & editing. **Linden Parkes:** Conceptualization, Writing - review & editing. **Jeggan Tiego:** Data curation, Formal analysis, Writing - review & editing. **Samuel Chamberlain:** Conceptualization, Writing - review & editing. **Karyn Richardson:** Data curation, Project administration, Writing - review & editing. **Rebecca Segrave:** Conceptualization, Project administration, Funding Acquisition, Writing - review & editing **Murat Yücel:** Conceptualization, Funding Acquisition, Writing - review & editing.

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7.3. Supplementary Materials and Methods

Participants

Participants were recruited from the general community. This was done through flyers and online advertisement, primarily targeted at the Monash University Clayton and Caulfield campuses and surrounding areas. As majority of individuals with OCD- and addiction-related behaviors are not in clinical care, this was considered an appropriately representative area. These samples are also considered diverse with respect to race/ethnicity and sex, though generally younger with respect to age.

Participants had no lifetime history of DSM-5 defined psychotic illness, bipolar affective disorder (I and II), bulimia nervosa or anorexia, severe substance use disorder, learning difficulty, ADHD or other condition involving cognitive impairment as the primary feature. Current thoughts of suicide or self-harm, as well as severe anxiety or depression were excluded. There was no history of neurological illness or brain injury, major medical conditions, endocrine disorder, adrenal dysfunction, autoimmune disorder, or other conditions known to have a direct effect on the HPA-axis. Participants were also excluded if currently using psychoactive medications (i.e. antidepressants, mood stabilizers, antipsychotics, benzodiazepines, or other psychiatric medications) or glucocorticoid medications.

Materials

Screening measures. Screening for inclusion/exclusion criteria involved the MINI International Neuropsychiatric Interview for DSM-5 (M.I.N.I; (1), the 7-item Generalized Anxiety Disorder (GAD-7; (2), 9-item Patient Health Questionnaire (PHQ-9; (3) and Y-BOCS compulsivity subscale (4).

Compulsivity. Participants were first presented a thresholding question to determine current engagement in a behavior, evident over the past three months. For more occasional behaviors (i.e. gambling and drinking alcohol), participants were asked "*Have you gambled in the past 3 months?".* For everyday behaviors (i.e. checking, symmetry, cleaning, alcohol consumption and binge-eating), the thresholding question asked about excessive engagement in the behavior. For example, *"In the past 3 months, have you needed to eat food excessively, even though you were not hungry?".* If participants endorsed a behavior at thresholding, they were then shown an adapted version of the Y-BOCS. The Y-BOCS is a 10-item self-report scale. The first 5 items ask about thoughts related to a behavior (e.g. "*How much of your time was occupied by thoughts of…*") and second five items are related to the behavior itself (e.g. "*How much time did you spend on….*"). Individual items of the Y-BOCS were tailored to each behavioral domain being measured. For example, "*How anxious or distressed do you feel if prevented from <u>eating</u>?"* or *"How anxious or distressed do you feel if prevented from <u>drinking alcohol</u>?".* Participants responded on 5-point Likert scale ranging from 0 - 4 and scores can range from 0 to 40. Higher scores are indicative of greater of severity obsessions and compulsions related to a behavior.

Behavioral Avoidance. The behavioral avoidance subscale is made up of 11-items. Participants respond on a 6-point Likert scale ranging from 1(strongly disagree) to 6 (strongly agree). Scores can range from 11 to 66. Higher scores are indicative of increased use of behavioral avoidance strategies to avoid uncomfortable experiences (e.g. "*I work hard to avoid situations that might bring up unpleasant thoughts and feelings in me"*).

Stress. It is a 10-item scale, to which participants respond 0 (never) to 4 (very often). Scores range from 0-49 and higher scores indicate greater perceived stress (e.g. "*how often have you been upset because of something that happened unexpectedly")*.

Self-reported symptoms: used for validation of subtypes. Anxiety and depressive symptoms were measured using the State-Trait Anxiety Inventory Y2 (STAI-Y2; (5) and Centre for Epidemiologic Studies Depression Scale Revised (6), respectively. Constructs which have previously been linked to transdiagnostic compulsivity were also assessed, including intolerance of uncertainty and impulsivity (7). This was done using the Intolerance of Uncertainty Scale (IUS; (8) and the negative and positive urgency subscales of the UPPS-P Impulsive Behavior Scale (9).

Neurocognitive measure: Full description of cognitive task (BeanFest). Participants begin the game with 50 points and aim to win by reaching 100 points and avoid losing by reaching 0 points. Approaching positive beans adds points (+10), while approaching negative beans loses points (-10). Avoiding a bean results in no net loss/gain. Participants receive feedback about the beans value irrespective of whether they decide to approach or avoid it. The beans vary systematically in terms of shapes (i.e. circular to oblong) and how many speckles they have. In the learning phase, participants complete three 36-trial blocks to learn the valence of 36 "game" beans. In the test phase, participants randomly view the 36 game beans, as well as 64 "novel" beans and are asked to indicate if that bean is "helpful" or "harmful". For further task information, see (10).

Neurohormonal measure: Saliva sampling protocol and analysis. Participants were asked to collect six saliva samples at home on two consecutive typical working days (awakening (t_0), 30-minutes after awakening (t_{30}) and 45-minutes after awakening (t_{45})). During saliva collection period, they were instructed to take nil by mouth other than water, and not to smoke or brush their teeth. Samples were placed in participants' home freezer as soon as possible after collection of saliva and transferred to the laboratory in insulated cold packs to be stored at - 20C until assay. Participants were asked to fill in a record sheet on

each day recording awakening time and time of collection of saliva samples. Responses were screened for inconsistencies between awakening time and time of first saliva collection on each day. No participants reported a discrepancy of greater than 5 minutes.

Samples were thawed and centrifuged at 1500rpm x g for 15 minutes. Cortisol concentration was determined by salivary cortisol immunoassay kit developed by Salimetrics LLC (USA). Sensitivity = 0.003 µg/dL. Salivary cortisol correlated well with matched serum cortisol concentrations (r = 0.91). Intra and inter-assay variations were both below 5%.

To address the problem of non-adherence to the requested saliva sampling regime, suspected non-adherence was examined by identifying CAR profiles showing no cortisol rise from waking sample to either the 30 or 45 min samples post awakening (11). Such cases were identified as missing data. As CAR was measured on two consecutive days, when there was a missing data point for one day, the alternative day was used to determine the participants CAR. Where two days were available, an average value of both days was used.

Detailed image pre-processing. Dicom images were firstly converted to nifty (i.e., analyse format) using dcm2niix, and organized in BIDS format (https://bids.neuroimaging.io/). The following processed were conducted by fMRIPrep [version 1.1.1 (12,13)] on a CENTOS 7 cluster computing system (www.massive.org.au). And the details below were adapted from the method session of fMRIPrep report.

T1-weighted image: The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (14), distributed with ANTs 2.2.0 (15), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation (16,17) of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF),

white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast [FSL 5.0.9, RRID:SCR_002823, (18)]. Volume-based spatial normalization to standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0), using brain-extracted versions of both T1w reference and the T1w template.

Resting state functional MRI: First, a reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. A deformation field to correct for susceptibility distortions was estimated based on fMRIPrep 2019s fieldmap-less approach. The deformation field is that resulting from co-registering the BOLD reference to the same-subject T1w-reference with its intensity inverted (19,20). Registration is performed with antsRegistration (ANTs 2.2.0), and the process regularized by constraining deformation to be nonzero only along the phase-encoding direction, and modulated with an average fieldmap template (21). Based on the estimated susceptibility distortion, an unwarped BOLD reference was calculated for a more accurate co-registration with the anatomical reference. The BOLD reference was then co-registered to the T1w reference using flirt [FSL 5.0.9, (22)]. Co-registration was configured with nine degrees of freedom to account for distortions remaining in the BOLD reference. Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 5.0.9 (22). BOLD images were slice-time corrected using 3dTshift from AFNI 20160207 (23). The BOLD time-series were resampled onto their original, native space by applying a single, composite transform to correct for head-motion and susceptibility distortions. These resampled BOLD time-series will be referred to as preprocessed BOLD in original space, or just preprocessed BOLD.

The BOLD time-series were resampled into standard spaces, correspondingly generating the following spatially-normalized, preprocessed BOLD images: MNI152NLin2009cAsym. A reference volume and its skull-stripped version were generated using a custom methodology of fMRIPrep. Automatic removal of motion artifacts using independent component analysis (ICA-AROMA), (24) was performed on the preprocessed BOLD on MNI space time-series after removal of non-steady state volumes and spatial smoothing with an isotropic, Gaussian kernel of 6mm FWHM (full-width half-maximum). Corresponding non-aggressively denoised images were produced after such smoothing.

Several confounding time-series were calculated based on the preprocessed BOLD: framewise displacement (FD), DVARS and three region-wise global signals. FD and DVARS are calculated for each functional run, both using their implementations in Nipype (following the definitions by (25). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction [CompCor, (26)]. Principal components are estimated after high-pass filtering the preprocessed BOLD time-series (using a discrete cosine filter with 128s cut-off) for the two CompCor variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 5% variable voxels within a mask covering the subcortical regions. This subcortical mask is obtained by heavily eroding the brain mask, which ensures it does not include cortical GM regions. For aCompCor, components are calculated within the intersection of the aforementioned mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run (using the inverse BOLD-to-T1w transformation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the k components with the largest singular values

are retained, such that the retained components\u2019 time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. All resamplings can be performed with a single interpolation step by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (27). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Detailed image post-processing: SPM12 (matlab r2018) was used to conduct the voxel wise statistical analysis. Firstly, all the output images of amygdala-based rs-FC maps from preprocessing were used to generate the rs-FC patterns for each group using three separate one-sample t-tests. For illustration purposes, a stringent threshold (T = 7.7, p = 1e-09) was applied for three subgroups. Secondly, to further statistically explore the group differences, the F-test mode is used (F-test with controlling covariance on SPM12), with group as main factor (3 levels) and controlling for age and sex. F-contrast was setup to detect any group differences among three subgroups. Post-hoc independent t-tests were conducted to examine directional differences between each of the subgroups. For each comparison, results were thresholded at uncorrected p-value < .001 with cluster size > 10,

then corrected for multiple comparisons error at the cluster level of $p < .05$, using family wise error (FWE) correction. Only $p_{FWE}<0.05$ regions were considered as significant.

7.4. Supplementary Results

Missing data, outliers and normality

Missing values create problems for clustering approaches and omitting entire cases with one missing domain decreases the sample size considerably. Therefore, before performing clustering, any missing values were approximated. Most participants accurately completed all measures, however some participants had missing data for the CAR due to saliva samples not being returned (n = 4, 8.89%) or suspected non-adherence to the requested saliva sampling regime (n = 2, 4.44%). This data was considered missing at random and approximated using Expectation Maximisation procedures (28). There were no other missing data. There was one univariate outlier in the data for the valence learning bias (z = 3.32), which was dealt with using winsorising (29). Multivariate outliers were not identified on the study sample with the critical value of Mahalanobis distance $\chi^2(5) > 20.51$, $p < .001$. Skewness and kurtosis were also examined for all variables to be entered into the cluster analysis. Skewness and kurtosis values were converted to z values, which ranged from – 0.40 to 1.46 and – 0.74 and 0.07 respectively. These values did not fall outside the critical value $z = \pm 2.58$, $p < .01$, indicating no deviations from normality (28). There was also no evidence of multicollinearity between variables.

Table S1.

Descriptive characteristics of measures entered into cluster analysis

Measure	Mean (*SD*); Range
Y-BOCS	16.76 (6.31); 5 – 31
MEAQ-BA	38.07 (9.80); 20 - 63
PSS	21.16 (4.98); 12 - 34
CAR salience (nmol/L)	.23 (.25); - .26 - .65
Valence learning bias	.09 (.24); - .38 - .60

Note: Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; MEAQ-BA = Multidimensional Experiential Avoidance Questionnaire Behavioural Avoidance subscale; PSS = Perceived Stress Scale; CAR salience = cortisol awakening response salience score, measured in nanomoles per litre (nmol/L).

Table S2.

Agglomeration schedule from hierarchical cluster analysis

Stage	Cluster Combined		Coefficients	Stage Cluster First Appears		Next Stage
	Cluster 1	Cluster 2		Cluster 1	Cluster 2	
1	24	25	0.112	0	0	8
2	11	18	0.341	0	0	16
3	15	16	0.611	0	0	15
4	20	35	0.991	0	0	16
5	3	5	1.5	0	0	26
6	27	32	2.036	0	0	24
7	26	40	2.592	0	0	18
8	23	24	3.166	0	1	11
9	42	44	3.801	0	0	29
10	39	41	4.452	0	0	32
11	22	23	5.135	0	8	25
12	28	30	5.868	0	0	25
13	2	4	6.672	0	0	19
14	10	21	7.522	0	0	17
15	13	15	8.379	0	3	20
16	11	20	9.471	2	4	31
17	10	31	10.656	14	0	27
18	26	29	11.867	7	0	32
19	2	7	13.102	13	0	30
20	13	14	14.36	15	0	31
21	33	34	15.851	0	0	37
22	37	38	17.347	0	0	35
23	6	9	18.909	0	0	30
24	27	36	20.592	6	0	35
25	22	28	22.301	11	12	28
26	3	45	24.087	5	0	34
27	10	12	26.011	17	0	40
28	17	22	28.821	0	25	33
29	42	43	31.808	9	0	38
30	2	6	34.886	19	23	36
31	11	13	38.38	16	20	37
32	26	39	41.955	18	10	41
33	17	19	46.727	28	0	41
34	3	8	51.78	26	0	39
35	27	37	56.851	24	22	40
36	1	2	62.199	0	30	38
37	11	33	69.939	31	21	42
38	1	42	77.911	36	29	39

39	1	3	86.497	38	34	44
40	10	27	95.338	27	35	42
41	17	26	110.94	33	32	43
42	10	11	134.632	40	37	43
43	10	17	162.337	42	41	44
44	1	10	220	39	43	0

Table S3.

Percentage (%) change in agglomeration coefficient and rationale for cluster selection

Cluster solution	% Change	Rationale
9	12.44	
8	11.40	
7	11.02	
6	10.22	
5	16.36	% change lower than average
4	21.36	increase larger than previous stage; stopping point
3	20.58	3 cluster is next favored solution
2	35.52	largest change for 2 cluster solution
1		
Average % change	17.36	

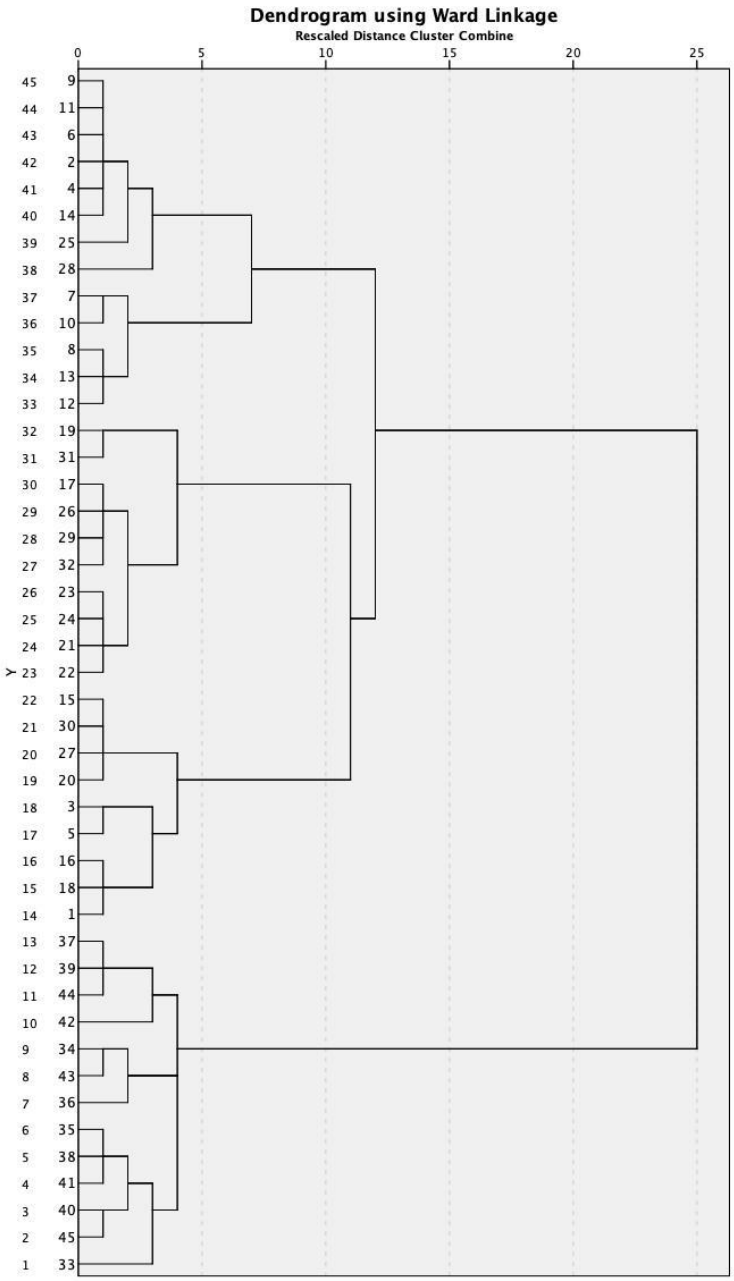

Fig S1: Dendrogram for hierarchical agglomerative method (Ward's method) with squared Euclidean distance. The x-axis represents the degree of dissimilarity between cases, measured via the squared Euclidean distance. The y-axis represents pairs of cases, where numbers refer to the SPSS line rather than subject ID.

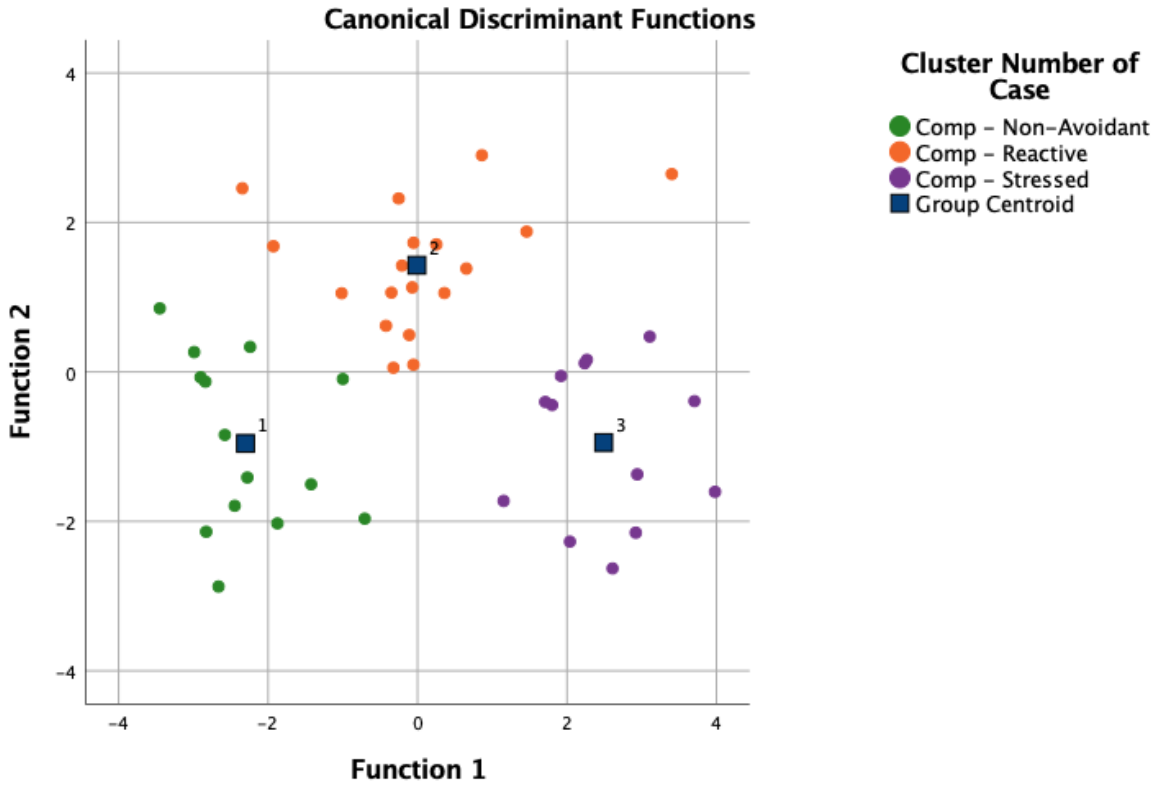

Fig S2. Three cluster solution plotted in discriminant function space.

Validation of final cluster solution: MANOVA's, ANOVA's and Chi-square tests

Subgroups were compared on demographic variables. A chi-squared test for independence indicated there was a significant association between sex and cluster membership, χ^2 (1, *n* = 45) = 6.65, *p* = .036, *phi* = .38. Sex was therefore included as a covariate in all subsequent analyses. There was no significant association between cluster and compulsion type (i.e. OC-related or behavior-related), χ^2 (1, *n* = 45) = 1.31, *p* = .52, *phi* = .52, or age, *F*(2, 42) = .41, *p* = .67.

In the assessment of subgroup differences, multivariate general linear models (GLM) with a factor of group (3: cluster 1, 2 or 3) and covariate of sex, yielded significant differences (*p* < .05) in compulsivity (i.e. Y-BOCS total, obsessions and compulsions subscales) and compulsivity-related variables (i.e. IUS, UPPS-P positive and negative urgency subscales), *F* (10, 76) = 8.41, *p* < .001; Pillai's Trace = 1.06, η_p^2 = .53. Tests of between-subjects effects indicated significant differences on the Y-BOCS total (*F*(2, 41) = 12.36, *p* <.001, η_p^2 = .38), Y-BOCS obsessions subscale (*F*(2, 41) = 11.55, *p* <.001, η_p^2 = .36), Y-BOCS compulsions subscale (*F*(2, 41) = 10.29, *p* <.001, η_p^2 = .33), IUS (*F*(2, 41) = 21.65, *p* <.001, η_p^2 = .51), UPPS-P negative (*F*(2, 41) = 6.93, *p* = .003, η_p^2 = .25) and positive (*F*(2, 41) = 9.77, *p* <.001, η_p^2 = .32) urgency subscales. Post-hoc with Bonferroni adjustment for multiple comparisons were used to identify group differences (Table S4). Subgroup 3 exhibited poorer outcomes on most measures of compulsivity and compulsivity-related variables when compared to subgroup 1 and 2. Subgroup 2 demonstrated higher levels of intolerance to uncertainty (IUS) and positive urgency (UPPS-P) in comparison to cluster 1.

Multivariate GLM also demonstrated significant differences on behavioral avoidance (i.e. MEAQ-behavioral avoidance subscale) and psychological wellbeing variables (i.e. PSS, STAI-Y2, CESD-R), *F* (8, 78) = 6.68, *p* < .001; Pillai's Trace = .81, η_p^2 = .41. Tests of between-

subjects effects indicated significant differences on the MEAQ-BA ($F(2, 41) = 14.84$, $p < .001$, $\eta_p^2 = .42$), PSS ($F(2, 41) = 24.79$, $p < .001$, $\eta_p^2 = .55$), STAI-Y2 ($F(2, 41) = 6.99$, $p = .002$, $\eta_p^2 = .25$) and CESD-R ($F(2, 41) = 12.91$, $p < .001$, $\eta_p^2 = .39$). Post-hoc comparisons for group differences are displayed in Table S4. Again, subgroup 3 showed significantly poorer psychological wellbeing than subgroups 1 and 2 across most measures. Subgroup 2 demonstrated significantly higher behavioral avoidance compared to cluster 1.

Univariate GLM with a factor of group (3: cluster 1, 2 or 3) and covariate of sex also yielded significant differences ($p < .05$) in CAR salience score, $F (2, 41) = 13.14$, $p < .001$, $\eta_p^2 = .39$ and valence learning bias, $F (2, 41) = 8.97$, $p = .001$, $\eta_p^2 = .30$. Post-hoc comparisons for group differences are displayed in Table S4. Subgroup 2 had a significantly higher CAR when compared to cluster 1. Subgroup 1 had a negative learning bias compared to subgroups 2 and 3, which both demonstrated positive learning biases.

Table S4.

Demographic and cluster profiles

Subgroup	1 (*n* = 14) Non-Avoidant *M (SD)*	2 (*n* = 18) Reactive *M (SD)*	3 (*n* = 13) Stressed *M (SD)*	Post hoc comparisons (*p* < .05)
Age	24.57 (4.86)	24.56 (4.90)	26.31 (7.77)	*p* = .52
Sex (m/f)	7/7	11/7	2/7	*p* = .036
Primary compulsion (Beh/OC)	8/6	6/12	4/9	*p* = .67
Compulsivity (Y-BOCS)				
Total	15.57 (5.60)	13.22 (4.62)	23.00 (4.20)	1 < 3; 2 < 3
Obsessions	7.57 (2.77)	6.39 (2.17)	11.00 (2.34)	1 < 3; 2 < 3
Compulsions	8.00 (3.16)	6.83 (2.81)	12.00 (2.20)	1 < 3; 2 < 3
Psychological wellbeing				
Behavioral Avoidance (MEAQ-BA)	30.36 (6.69)	37.78 (6.67)	46.77 (9.44)	1 < 2; 1 < 3; 2 < 3
Coping with stress (PSS)	18.14 (2.80)	19.28 (3.29)	27.00 (3.79)	1 < 3; 2 < 3
Anxiety (STAI-Y2)	40.29 (6.07)	42.83 (6.65)	49.69 (6.40)	1 < 3; 2 < 3
Depression (CESD-R)	8.93 (6.93)	7.22 (4.61)	23.23 (12.04)	1 < 3; 2 < 3
Compulsivity-related variables				
Intolerance of uncertainty (IUS)	25.00 (5.38)	32.28 (6.28)	40.31 (9.87)	1 < 2; 1 < 3; 2 < 3
Positive urgency (UPPS-P)	23.21 (6.87)	31.50 (6.00)	33.08 (6.21)	1 < 2; 1 < 3
Negative urgency (UPPS-P)	24.57 (6.21)	25.94 (3.84)	31.62 (3.89)	1 < 3; 2 < 3
Cortisol Awakening Response				
CAR salience	.027 (.22)	.394 (.18)	.210 (.19)	1 < 2
t_0	7.63 (5.02)	8.20 (4.21)	9.35 (5.19)	ns
MnInc	6.23 (3.07)	5.84 (3.31)	5.01 (5.81)	ns
Cognitive bias (BeanFest)				
Valence learning bias	- .093 (.15)	.213 (.23)	.100 (.20)	1 < 2; 1 < 3

Note: Beh = behavior-related compulsion (i.e. alcohol or eating); OC = obsessive-compulsive related (i.e. checking, symmetry or contamination); Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; MEAQ-BA = Multidimensional Experiential Avoidance Questionnaire Behavioral Avoidance subscale; PSS = Perceived Stress Scale; STAI-Y2 = State-Trait Anxiety Inventory Y2; CESD = Centre for Epidemiologic Studies Depression Scale Revised; IUS = Intolerance of Uncertainty Scale; UPPS = UPPS-P Impulsive Behavior Scale; CAR salience = cortisol awakening response salience score, measured in nanomoles per litre (nmol/L); t_0 = salivary cortisol on awakening in nmol/L; MnInc = Mean Increase in cortisol from awakening; ns = non-significant difference between groups.

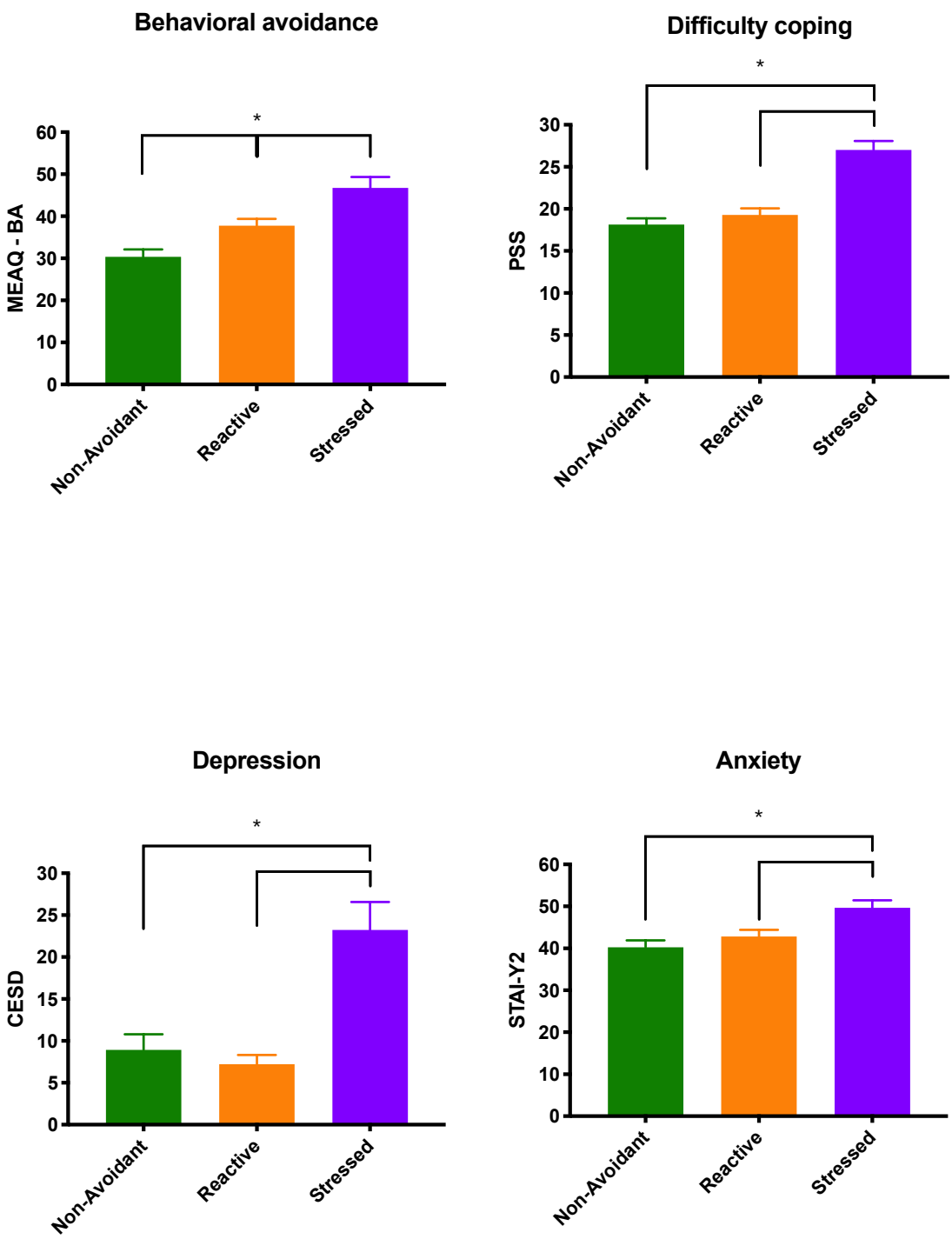

Fig. S3. Subgroup differences on psychological wellbeing variables. MEAQ-BA = Multidimensional Experiential Avoidance Questionnaire Behavioral Avoidance subscale; PSS = Perceived Stress Scale; STAI-Y2 = State-Trait Anxiety Inventory Y2 (trait); CESD = Centre for Epidemiologic Studies Depression Scale Revised. Bars represent group means and error bars represent standard error. * $p < .05$

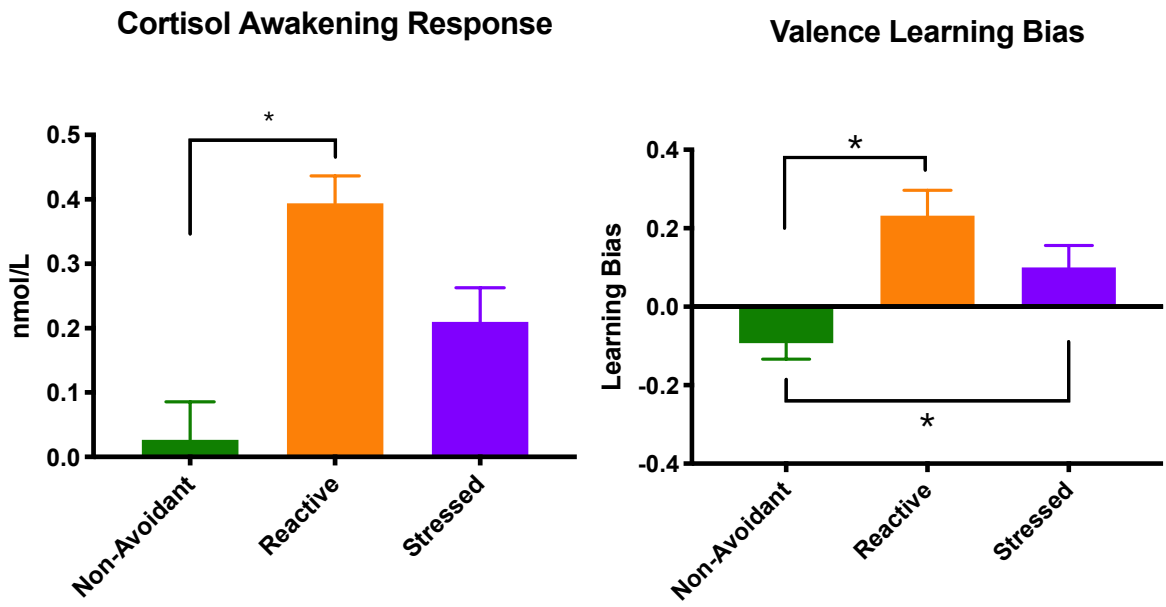

Fig. S4. Subgroup differences on cortisol awakening response and valence learning bias. Bars represent group means and error bars represent standard error. * $p < .05$

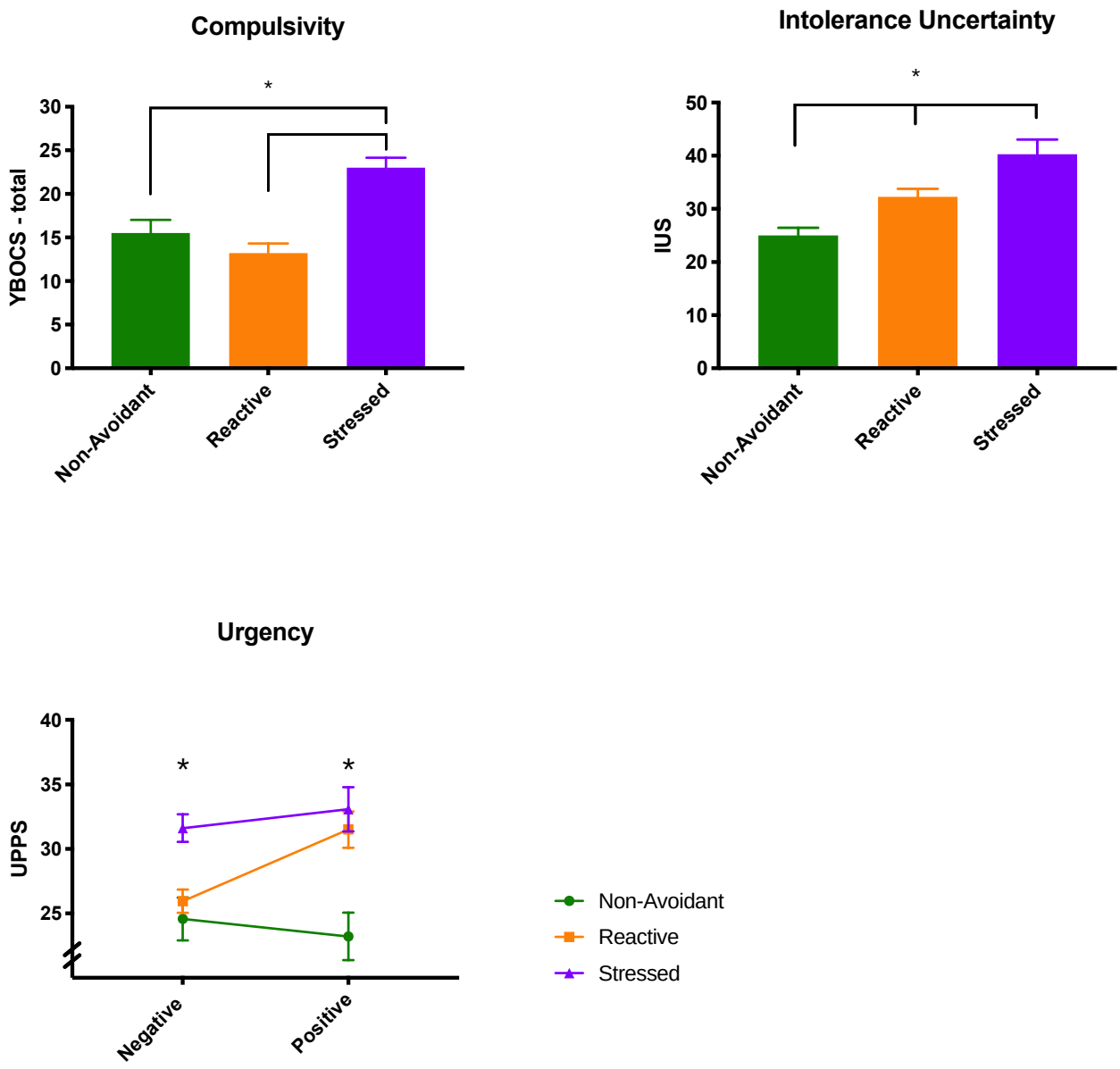

Fig. S5. Subgroup differences on compulsivity and compulsivity-related variables (i.e. intolerance of uncertainty and negative/positive urgency). IUS = Intolerance of Uncertainty Scale; UPPS = UPPS-P Impulsive Behavior Scale. Bars represent group means and error bars represent standard error. * $p < .05$

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CHAPTER EIGHT
8. General Discussion

8.1. Summary of key results

Study One in Chapter 6 explored the association between EA, psychological distress and transdiagnostic compulsive behaviour within the community, using structural equation modelling. Fulfilling the first main aim of the thesis, results showed that compulsive behaviour is highly prevalent even at the community level and that it is expressed across multiple behaviours for some individuals. This highlights the importance of investigating for multiple compulsive behaviours in clinical assessment and emphasizes the need to treat the underlying causes of compulsivity rather than the discrete behaviour.

Addressing another main aim, the findings revealed that EA is implicated transdiagnostically across addictive and OCD-related compulsive behaviours and clarified the mechanisms through which EA influences compulsive behaviour. Specifically, results revealed that EA positively predicted psychological distress, and that the relationship between transdiagnostic compulsivity and EA was fully mediated by psychological distress. This suggests that compulsive behaviours are a poor coping response to negative emotions and that a tendency toward poor emotion regulation strategies, such as EA, paradoxically increased the likelihood of distress. Overall, results of Study One underscore the importance EA as a potential treatment target for transdiagnostic compulsivity.

Study Two in Chapter 7 utilised clustering analysis, a statistical approach which identifies hidden phenotypes within an observational cohort. Measures from multiple dimensions (i.e. psychology, cognition, neurobiology) were integrated to explore for subtypes of compulsive behaviours. This study extended on Study One by integrating cognitive (i.e. punishment/reward learning biases) and neurobiological (i.e. CAR) measures of affective

processes, with psychological motivation for EA and stress. We identified three subtypes (i.e. compulsive – non-avoidant, - reactive and – stressed), each with a unique profile across measures of symptom severity, psychological motivation and coping, cognition and neurohormonal activation. Fulfilling second main aim of the thesis, these subtypes could be meaningfully interpreted and existed transdiagnostically, suggesting they we not better explained by diagnostic categories. Importantly, the subtypes appear to be biologically valid expressions, as they differed meaningfully in resting-state amygdala functional connectivity. Findings emphasize the need for further multidimensional cross-sectional research to determine which factors and systems are related to increased incidence of compulsive behaviour and can be used as objective markers of compulsivity.

8.2. Integrating results into compulsivity literature

Collectively, the contribution of these two experimental studies can be summarised into three main points.

First, from a psychological perspective, the link between avoidance coping, distress and compulsive behaviour stands out. The co-occurrence between these variables underscores the importance of emotion regulation models of compulsivity.

Second, from a neurobiological perspective, cognitive and biological systems implicated in punishment/reward learning, stress and affective processing are important for our understanding of compulsive behaviour. Interactions between these systems may constitute added risk or protection against compulsivity and be expressed at different stages of behaviour severity (e.g. subclinical, mild, moderate, severe).

Third, from a methodological perspective, incorporating multiple dimensions of functioning and concurrently examining them through clustering approaches, provides cross-sectional information on how different systems interact in psychopathology. In line

with the RDoC initiative, this approach ultimately demonstrates a new way for developing a taxonomy of mental disorders, based in underlying neuro-behavioural dimensions.

8.2.1. Experiential avoidance and the nature of its relationship to transdiagnostic compulsive behaviour

The first conclusion from this work is consistent with a relatively recent review on compulsivity (Figee et al., 2016), which identified negative reinforcement (i.e. avoidance of aversive or anxiety-inducing outcomes) as one of the key processes that drives compulsive behaviour. Our results expand on this by identifying EA as a psychological characteristic that makes individuals more prone to using behaviours to avoid uncomfortable experiences. Although previous studies have suggested a link between EA and compulsive behaviours (Dvorak et al., 2013; Litwin et al., 2017; Riley, 2014; Wetterneck et al., 2014; Williams, 2012), this link had not been explored transdiagnostically and has not been consistently found (Abramowitz, Lackey, et al., 2009; Manos et al., 2010), largely due to differences in the way EA is measured, conceptualised and statistically tested.

Results from Study One showed that EA and distress explained 41% of the variance in compulsive behaviour and that EA explained 40% of the variance in distress itself. Thus, a tendency to use avoidance strategies to manage distress is linked to increased likelihood of engaging in compulsive behaviour and an increased likelihood of experiencing distress. It is difficult to directly compare our findings to previous work, as majority of past research has used older measures to assess EA (i.e. the AAQ). The AAQ has come under scrutiny for being more akin to a measure of general distress (Tyndall et al., 2019; Wolgast, 2014). The MEAQ is thought to be a more valid representation of EA (Rochefort et al., 2018). Therefore, results from Study One will be compared with the two other investigations (Dvorak et al.,

2013; Litwin et al., 2017) which have used the MEAQ to examine EA and compulsive behaviour.

Consistent with our findings, the overarching outcome of both investigations was that EA predicts increased incidence of behaviour, which were emotional eating (Litwin et al., 2017) and alcohol use (Dvorak et al., 2013). Like Study One, Litwin et al. (2017) examined the relationship between negative emotionality (like our measure of distress), EA and compulsive eating. However, there was discrepancy between how EA was conceptualised. Litwin et al. (2017) conceptualised EA as state-based and thus placed it further downstream in the path analysis than negative emotionality. This led to the conclusion that negative emotions predict EA, which in turn predict compulsive eating behaviour. By comparison, in our investigation, EA was placed further upstream, predicting psychological distress and in turn compulsive behaviour. As the MEAQ assesses EA as a trait-like function, represented as an unwillingness to tolerate negative emotions, it seemed more fitting to include it as the first predictor in the model. Competing models were evaluated (including one where distress served as the main predictor) and our results favoured the model whereby EA → distress → compulsivity.

Discrepancies as to whether EA is considered a mediator, moderator or first predictor in a model does not necessarily impact the broad clinical implications, however it can have ramifications for overall model interpretation and theoretical understanding. For instance, in terms of clinical implications, both Litwin et al. (2017) and our study concluded that interventions targeting EA, such as ACT, would be effective in treating compulsive behaviours. ACT teaches individuals to accept the presence of uncomfortable emotions rather than seeking ways to avoid them. However, in terms of theoretical understanding, the Litwin et al. (2017) findings would lead to the conclusion that EA is a strategy that occurs

in response to distress, while from our study, it would be concluded that EA is a core belief that can *lead to distress*. While there is likely truth to both pathways, it is important to examine alternate models and determine best fit for the outcome behaviour, as this may have more nuanced implications for clinical treatment and future research. For example, the way in which the clinician interviews for EA behaviour (e.g. "what do you do when feelings of anxiety arise?" versus "do you wish for a life free of uncomfortable emotions?"). Moreover, future investigations may elicit null findings if EA is incorrectly placed in the model and alternative pathways are not investigated.

The study by Dvorak et al. (2013), assessed EA in relation to alcohol use and motives for alcohol use within the context of PTSD. This study was consistent with our investigation in that EA was included further downstream in the path analysis and thus considered more trait-like. However, key differences were that they did not assess for the presence of negative emotionality/distress and EA was broken down into its various lower order constructs, rather than as one overarching construct. Key to experientially avoidant behaviour is the presence of unwanted/uncomfortable emotions. It is therefore important to assess if distress is present, as experientially avoidant behaviour may be suppressed when distress is absent.

An advantage of the Dvorak et al. (2013) study was that EA was investigated in terms of its six lower order constructs (i.e. behavioural avoidance, distress aversion, procrastination, distraction & suppression, repression & denial, and distress endurance). By doing so, they were able to determine that distress aversion, procrastination and distress endurance were the most relevant for understanding drinking behaviour in this population group. Although our Study One was more interested in linking the overarching concept of EA to the overarching concept of transdiagnostic compulsivity, some insights can be gleaned by

looking at correlations between the lower order constructs of EA and the different compulsive behaviours (as presented in Chapter 7, Supplementary Material, Table 3).

Firstly, while the higher-order construct of EA was significantly correlated with all compulsive behaviours, irrespective of the type of behaviour, the lower-order constructs were differentially related, as was found in the Dvorak et al. (2013) study. For instance, compulsive behaviour related to eating was most highly correlated with EA constructs of distress aversion, procrastination and distress endurance, while compulsive behaviour related to contamination concerns was correlated with behavioural avoidance, distress aversion and distraction & suppression. Like Dvorak et al. (2013), we found drinking behaviour to be most strongly related to distress aversion and repression & denial. This demonstrates that while overall EA is positively related to compulsive behaviour, there may be subtle differences in the nature of EA (e.g. avoiding distress altogether or putting off negative emotions until later) for different types of behaviours. While this was outside the main aim of Study One, and therefore not a featured discussion in the manuscript, it is important to consider these subtleties to help inform more individualised treatments. Future research may investigate the profiles of lower order EA constructs across various compulsive behaviours.

The link between EA, distress and compulsivity was evident once more in Study Two (presented in thesis Chapter 7). Of the three multidimensional subtypes that emerged, our "compulsive -stressed" subtype was differentiated by the highest levels of compulsive behaviour, EA and stress. This is consistent with the findings from Study One which demonstrated a positive relationship between compulsivity, EA and distress. Given some lower order EA constructs appeared more relevant than others for understanding compulsive behaviour, we chose to specifically focus on the lower-order construct of

behavioural avoidance for Study Two. This was selected because it captures the tendency to use behaviours/actions to manage negative emotions. Correlations from Study Two (Appendix 1: Table 1) revealed lower order constructs of distress aversion, distress endurance and behavioural avoidance all correlated with compulsivity, while constructs procrastination, distraction & suppression and repression & denial showed no correlation. This supported the decision to focus on a specific type of EA, which was statistically and theoretically relevant for the research question, rather than using the overarching EA score. Using the overall score may have introduced additional noise through the inclusion of questions related to types of EA not particularly relevant for compulsive behaviour.

In sum, the results from Studies One and Two both highlight the need to consider maladaptive emotional regulation strategies, like EA, when investigating drivers of compulsive behaviour. While there is now good evidence linking the overarching concept of EA to compulsive behaviour, these results indicate future research should focus on specific types of EA. Moreover, the causal association between EA and compulsivity requires longitudinal research to fully determine the nature and the direction of relationships.

8.2.2. Cognitive and neurobiological systems linked to experiential avoidance and transdiagnostic compulsive behaviour

Our knowledge of the underlying systems that contribute to compulsive behaviour is still developing, and thus understanding of how these various systems interact with each other is lacking. The work from Study Two, presented in thesis Chapter 7, was a step toward addressing this gap, investigating how systems associated with stress, emotion regulation and affective processing interacted in the context of compulsive behaviour.

Study Two used a statistical clustering approach to form three distinct subtypes of compulsive behaviour based on multidimensional indicators. Three naturally occurring

subtypes emerged which exhibited unique and interpretable profiles across the various levels of function and demonstrate consistencies with other areas of research. The highest level of compulsive behaviour was seen in subgroup (CS), which was also differentiated by high avoidance and stress, supporting the notion that these constructs co-occur. This is consistent with previous with-in diagnosis findings linking elevated stress to increased pathological repetitive behaviour in addictions (Barker & Taylor, 2014; Moore, Sabino, Koob, & Cottone, 2017; Schwabe, Dickinson, & Wolf, 2011) and OCD (Adams et al., 2018). It is also consistent with findings from Study One and other previous literature (Dvorak et al., 2013; Litwin et al., 2017) showing behavioural avoidance tendencies co-occur with severer compulsive behaviour presentations and elevated stress.

In Study Two, BeanFest (Fazio et al., 2015) was used to assess individual differences in learning from rewards versus punishments. The results showed that, while there was no direct correlation between learning biases and compulsive behaviour, the subgroups who had higher levels of compulsivity (and avoidance, stress, anxiety and depression) exhibited a positive learning bias. Large-scale studies have shown that within the general population there is a bias toward attending to negative stimuli on the task and that positive biases are less common (Fazio et al., 2015). Although the positive learning bias exhibited in the CS subgroup was weak, this remains consistent with the reasoning that these individuals tend to weigh approach (reward) learning more so that punishment learning. By comparison, the subgroup that exhibited the lowest levels of depression and anxiety (i.e. CNA) exhibited the only negative learning bias of the subgroups. Again, this was only a weak negative learning bias, but it suggests that biasing attention more toward negative stimuli is not necessarily a sign of psychopathology. At extreme levels the negative learning bias may be associated with depressive symptoms (Conklin et al., 2009; Pietri et al., 2015; Shook et al., 2007),

however at more mild-moderate levels it may be protective, as the individual is more receptive to negative feedback in the environment and can adjust their behaviour accordingly.

Further insights can be gained by interpreting the affective learning bias within the context of other aspects of the subgroup profiles. For instance, consider the CR subgroup which demonstrated the strongest positive learning bias, albeit only mild levels of compulsive behaviour. While a strong positive learning bias may constitute some risk for compulsive behaviours, when coupled with good perceived coping (i.e. low self-reported stress) and an elevated CAR (thought to assist with active coping; Steptoe & Serwinski, 2016), the risk may be diminished as these other variables could serve as protective factors. By comparison, the CS subgroup had a positive learning bias coupled with poor perceived coping and a lower CAR, thus possibly contributing to higher levels of compulsive behaviour. Taken together, affective learning biases appear to explain elements of the symptom presentation in compulsivity. Further research could explore if training learning biases toward more neutral (or mildly negative) levels influences compulsivity and mood-related psychopathology.

The inclusion of the neurobiological measure, CAR, also generated interesting insights. To recount, the CAR is elevated in individuals experiencing more stress in their day-to-day life, however an elevated CAR may serve a protective role, whereby it prepares the individual to cope with upcoming challenges (Powell & Schlotz, 2012). Moreover, the relationship between the CAR and coping appears to be inversely related and it starts to paradoxically decrease after stressors have mounted to a certain point (Duan et al., 2013; MacDonald & Wetherell, 2019), likely reflecting a threshold after which the HPA-axis is downregulated (Veen et al., 2011).

Therefore, the elevated CAR and low self-reported stress in the CR subgroup was interpreted as reflecting the link between increased CAR and active coping with the demands of the day. As the self-reported measure of stress assessed the *distress response to stress*, a low score can be interpreted as either minimal daily stressors present or reduced distress in response to daily stressors. The elevated CAR in this subgroup suggested that biologically there are increased demands being placed on the individual, despite this not being apparent on self-report measures. Comparatively, the CS subgroup exhibited only a moderately elevated CAR relative to other subgroups, which could reflect the reduction in the CAR that occurs in more severely stressful conditions where the individual is not coping well. This highlights the merit of including multidimensional, biological measures, particularly within the context of compulsivity. While individuals may be successful at avoiding negative states through the use of compulsive behaviours and thus may not acknowledge feeling stressed, there may still be a mood-related undertone driving the behaviour (Zsuzsika Sjoerds, Luigjes, van den Brink, Denys, & Yücel, 2014). The inclusion of neurobiological measure CAR helped to identify the mood-undertone occurring in the subgroups which may have been overlooked otherwise.

The results of Study Two also bring a remarkable contrast to light, namely, a stepwise decrease in amygdala resting-state functional connectivity (rs-FC) from the CNA subgroup to the CR subgroup, and from the CR subgroup to the CS subgroup. Surprisingly very few studies have investigated amygdala rs-FC within the context of compulsive behaviours and the available findings have been inconsistent in terms of the direction of difference found (i.e. whether rs-FC is generally increased or decreased).

Our results revealed that the subgroup with the greatest levels of compulsive behaviour (i.e. stressed subgroup) had the least functionally connected amygdala. This is consistent

with research showing that individuals with OCD have widespread decreased rs-FC in the limbic network when compared to healthy controls (Göttlich et al., 2014). Decreased connectivity of limbic regions with other cortical and sub-cortical regions is related to cognitive abnormalities observed in OCD, including detecting emotional salience and biases in the processing of rewards versus punishments, as well as difficulties with re-appraisal of emotional stimuli (Göttlich et al., 2014). This interpretation is also consistent with the elevated behavioural avoidance tendencies (i.e. poor emotional regulation strategy) evident in the CS subgroup, which suggested this subgroup had emotional regulation and re-appraisal difficulties.

By comparison, findings from substance-related compulsive behaviours have been more mixed and are somewhat in contrast to the subgroup profiles found in Study Two. In one recent investigation, *increased* rs-FC in the amygdala-striatal network was observed in alcohol dependent individuals compared to controls (Zhu et al., 2017), while another study found that alcohol misuse was related to *decreased* amygdala connectivity with the dACC (Hu et al., 2018). This suggests the relationship between compulsive behaviour and amygdala rs-FC may not be as simple as there being widespread reductions in amygdala connectivity, but that the direction of difference (i.e. increased or reduced) is dependent on the region with which the amygdala is connected. For example, for behaviours which are highly reward driven, such as substance use, it may be reasonable to expect stronger co-activation between the emotion and reward nodes of the brain (i.e. limbic and striatal respectively; Zhu, Cortes, Mathur, Tomasi, & Momenan, 2017), and weaker co-activation between emotion and cognitive control regions of the brain, such as the dACC (Hu et al., 2018). Despite this, the overarching finding from Study Two was the apparent decrease in amygdala rs-FC between the subgroups (CS < CR < CNA), with no evidence of stronger co-

activation between amygdala and other regions being linked to poorer outcomes on measures. Discrepancies are likely due to research from past investigations comparing diagnostic categories (i.e. pathological versus healthy controls), while our subgroups are formed based on multidimensional variables, all of which have their own relative relationship with amygdala FC.

In interpreting the amygdala rs-FC differences between each of the subgroups, it is also important to take into consideration the impact of mood and stress. There were clear mood-related differences between the subgroups and mood is highly related to amygdala function and connectivity. In general, mood-related concerns tend to be associated with reductions in amygdala rs-FC, as seen in studies comparing healthy controls to individuals with depression (Ramasubbu et al., 2014; Tang et al., 2018) and anxiety disorders (Hahn et al., 2011; Liu et al., 2015). Moreover, increased functional coupling between the amygdala and frontal regions has been linked to reductions in anxiety (Kim, Gee, Loucks, Davis, & Whalen, 2011) and increased subjective happiness (Sato et al., 2019). This is consistent with the finding from Study Two, whereby the CS subgroup exhibited overall reductions in amygdala rs-FC and had the highest levels of depression, anxiety and stress. Widespread decreased functional coupling between the amygdala and other brain regions likely reflects disrupted communication between bottom-up emotion generative networks and top-down control networks, and a predisposition to emotion driven psychopathology.

Figure 2 from Chapter 7 revealed the CR subgroup had moderate (albeit widespread) reductions in amygdala rs-FC, evidenced by greater amygdala rs-FC compared to the CS subgroup and reduced rs-FC compared to CNA subgroup. Abnormalities in reward versus punishment learning and emotional regulation have been linked to reduced amygdala rs-FC in OCD (Göttlich et al., 2014), which is consistent with the strong learning bias towards

reward, moderately elevated behavioural avoidance tendencies and reduced amygdala rs-FC characterising this subgroup. However, the only region that was statistically significant in the CR subgroup compared to the other subgroups was the left superior parietal lobe (SPL). The CR group demonstrated significantly reduced amygdala-SPL connectivity compared to the CNA subgroup, suggesting the co-activation between these regions was particularly un-synchronized. Findings from task-based fMRI studies have shown that amygdala connectivity with superior parietal regions is related to attention deployment and re-appraisal of emotional stimuli (Ferri, Schmidt, Hajcak, & Canli, 2016) and the successful down-regulation of emotion (Kanske, Heissler, Schönfelder, Bongers, & Wessa, 2011). Moreover, resting-state research has found decreased amygdala-parietal connectivity in patients with depression (Ramasubbu et al., 2014), further supporting that abnormalities in the connectivity between these regions is linked to disruptions in the modulation of affective processing. This indicates that at a neurological level, the CR subgroup may have disrupted affective processing, which is supported by psychological and cognitive aspects of the profile, including the elevated self-report behavioural avoidance tendencies and reward learning bias.

The other characteristic of the CR subgroup worth considering within the context of amygdala rs-FC is the CAR. There are clear links between the amygdala and biological cortisol production. For example, amygdala relativity to emotional stimuli is amplified when an individual's cortisol levels are increased (Klimes-Dougan et al., 2014). Moreover, connectivity between the amygdala and other subcortical regions, such as the hippocampus, have been shown to mediate the relationship between daily cortisol production and anxiety (Hakamata et al., 2017). However, when considering the CAR specifically, research has failed to find a direct relationship between the CAR and amygdala rs-FC (Golkar et al., 2014), albeit

there is surprisingly very little research investigating this link, thus making it difficult to draw conclusions. Nonetheless, an elevated CAR is representative of a mood-related biological undertone (e.g. preparing for stressors) and the decreased amygdala rs-FC represents disruptions in affective processing. While these two systems may not be directly inter-related, together they may constitute additive risk for compulsive behaviour.

Viewed as a whole, Study Two results support the existence of naturally occurring transdiagnostic phenotypes of compulsive behaviour. Importantly, the phenotypes are grounded in underlying neurobiology and the profiles of each phenotype can be meaningfully interpreted within the context of our current understanding of compulsive behaviour. The profiles generate new considerations into how different systems may interact with each other to provide added risk or protection against problematic repetitive behaviours.

8.2.3. Understanding compulsive behaviour: transdiagnostic and multidimensional approaches

Although compulsivity is gaining considerable interest in the research literature, this area is still very much in its infancy. For instance, it is only recently that a widely accepted definition of compulsivity has been proposed (Luigjes et al., 2019). As such, there is considerable variability in the way transdiagnostic 'compulsivity' has been measured, with studies often reverting to the measurement of peripherally related self-report constructs, such as obsessionality and intolerance of uncertainty (Parkes et al., 2019; Tiego, Oostermeijer, et al., 2019). This is problematic as these measures do not capture compulsivity itself, but rather overlapping (albeit separate) constructs, thus reducing the validity of outcomes and inferences drawn.

Studies One and Two demonstrated an alternative approach to capturing compulsivity across a variety of behaviours, which sought to minimise the biases of current approaches, while still allowing for compulsivity to be captured on one measurement scale. The Y-BOCS has previously been adapted to measure different domains of behaviour outside of OCD-related obsessions and compulsions (Anton, Moak, & Latham, 1996; Fedoroff, Sobell, Agrawal, Sobell, & Gavin, 1999; Jardin, Larowe, Hall, & Malcolm, 2011; Yee, Serrano, Kando, & McElroy, 2019), although this is the first time it has been used to assess a variety of different behaviours at one time. This approach was advantageous as it allowed us to capture aspects of compulsivity relevant to the current proposed definition, including the behavioural component (i.e. repetitive acts with reduced control) and the mental component (i.e. an awareness that the behaviour is not in line with one's goals; Luigjes et al., 2019). Moreover, all behaviours were measured on the same scale meaning an overall score of 'compulsivity' could be elicited based on the severity of behavioural and mental components, and irrespective of the type of behaviour itself (i.e. gambling, eating, shopping etc.). Despite this, there were still disadvantages associated with this method. In study one (Chapter 6; Table 2), some behaviours (i.e. shopping, gambling) tended to result in lower overall Y-BOCS scores, while others much higher (i.e. symmetry). This questioned whether the behaviours were all equally represented on the YBOCS scale, or if there were underlying biases towards OCD-like over addiction-like behaviours, despite attempts to adapt questionnaire items to suit the specific behaviour. For example, on the question "how much time do you spend performing X?", it is likely easier to score higher on everyday/accessible behaviours (e.g. cleaning, eating) than it is for less regular behaviours (e.g. drinking alcohol, gambling, shopping). Future research is needed to develop more fit-for-purpose measurement tools.

RDoC is very open-ended and one of the challenges is finding an analytic approach that integrates very different and independently measured data, from dimensions ranging from brain circuits, neurobiology, cognition, and self-report. Grisanzio & colleagues (2018) demonstrated a solution to this challenge, by utilising a data-driven method to explore transdiagnostic mood-related symptoms across multiple levels of function. Study Two adopted a similar approach and, consistent with Grisanzio et al. (2018), found that distinct subtypes emerge, which are differentially expressed across the multiple levels of function and exist along a spectrum of behaviour severity (i.e. low, intermediate and severe). This adds support for clustering approaches as a way to conduct integrative science in line with the RDoC initiative.

Study Two extended on Grisanzio et al. (2018) by attempting to validate subtypes within brain-imaging. The observation of rs-FC differences between each of the subgroups suggested that there were underlying functional connectivity differences between the groups, thus grounding findings in neurobiology. This approach is consistent with the RDoC conceptualisation that mental disorders are disorders of brain circuitry. Of note, Study Two had a considerably smaller sample size (45 versus 420 participants) compared to Grisanzio et al. (2018). One of the main limitations of a small sample size in cluster analyses is that smaller clusters or phenotypes may not be detected and are instead merged into larger clusters, thus leading to poorer differentiation and identification of existing phenotypes. As Study Two was the first of its kind in a compulsive population, we accepted this limitation and sought to identify larger clusters. However future investigations should look to include larger samples in order to detect smaller clusters that may have been overlooked in our investigation.

8.3. Thesis Achievements, Limitations and Future Work

This work expands the view of how compulsive behaviour is conceptualised and understood. The multidimensional markers identified, which likely contribute to the manifestation of compulsivity, are of relevance in elucidating the mechanistic processes of compulsive behaviour. In the following sections, the main achievements, as well as limitations and potential future work, will be addressed. While there will inevitably be some overlap here with the limitations discussed in the individual publications, here the focus will be on the broader limitations of the thesis.

First, given the relative infancy of the field, there are very few accepted measures available for assessing transdiagnostic compulsive behaviour, and thus additional 'tools' for this toolkit are welcomed. Nevertheless, adapting the Y-BOCS to each behaviour and summating the scale to provide an overall indication of compulsivity, is a technique that has not previously been validated in the literature. As mentioned above, there are questions around its validity to capture compulsivity equally across all behaviours. Knowing that the present results may be confounded by possible biases in the outcome measure of compulsivity, it would be important for future research to explore the validity of this measurement technique against other newly developed measures of compulsivity, such as the Cambridge-Chicago Compulsivity Trait Scale (Chamberlain & Grant, 2018). It would also be important to consider the proposed definition of compulsivity (Luigjes et al., 2019) in the future development of compulsive behaviour assessment tools and consider how key aspects of the definition can best be captured.

Second, one of the main advantages of multidimensional investigations is the integrated observation of multiple processes, thus shedding light on how they interact in the context of compulsivity. However, in light of the discussed limitations (i.e. impact of

small sample sizes on clustering approaches), future studies should examine the replicability of the findings in bigger samples sizes using a wider variety of outcome measures (e.g. additional cognitive tasks, brain-imaging measures etc.) to help identify other possible phenotypes. The importance of replication in clustering analyses cannot be understated, as there is a risk that clustering may reveal subtypes that do not reflect underlying behavioural and biological differences, but are rather the product of data error variance (Dinga et al., 2019). Precautions were taken to assess the validity of subtypes. Mainly, robust and meaningful differences on amygdala rs-FC indicated subgroups were valid representations of underlying neurobiological variance.

Last, our results identified potential vulnerability markers, indicated by measures linked to processes that are likely related to compulsive behaviour. However, these ideas require a degree of speculation, as the exact role of some outcomes in compulsivity is still a matter of debate. For example, there is still debate over the exact function of the CAR (Fries et al., 2009; Steptoe & Serwinski, 2016), and while it has an established link to stress (Steptoe & Serwinski, 2016), awakening cortisol is yet to be identified as a process specifically relevant for compulsivity. Further, little is known about what stages of disorder onset, progression and symptom improvement these outcomes are most relevant. Therefore, longitudinal and intervention studies are needed to clarify the existing findings and examine how these systems develop, change and interact over time. This would enable inference of causal and maintenance factors for compulsive behaviour.

In sum, and considering the existing limitations, the achievements of the presented studies strengthen our understanding of transdiagnostic compulsive behaviour and offer new methods for future lines of investigation, although will require replication.

8.4. Concluding Statement

Taken together, it becomes clear that compulsive behaviour does occur transdiagnostically, irrespective of diagnostic boundaries, and that it exists on spectrum from absent, mild, moderate to severe, thus making it relevant for both people living with compulsive psychopathology and those throughout the general community who do not meet the threshold set by diagnostic criteria. Moreover, there are common underlying psychological, cognitive and neurobiological factors which drive OCD-like and addiction-like compulsive behaviours. However, models of compulsive behaviour and its causes are still being developed, and our current understanding remains relatively limited. The release of the RDoC offered new considerations for how to investigate psychopathology, calling for approaches that integrate findings from multiple levels of function to help build a more homogeneous picture of pathological behaviour. Given the high prevalence and burden of disease associated with compulsivity, the need to understand its causes cannot be understated. There is a pressing need for further multidimensional, cross-sectional research, such as the current studies, to identify factors that may contribute to compulsive behaviour.

The present work provides valuable new insights into possible underlying causes of compulsive behaviour and novel ways it can be assessed. It further reinforces the need for multidimensional, transdiagnostic approaches which integrate findings and show how underlying systems may function and interact. Moreover, the results provide preliminary indication of potential vulnerability and maintenance factors in the mild-moderate stages of compulsive behaviour. These are important stages clinically as they are promising targets for intervention to prevent progression to more severe behaviour presentations. Finally, the present results underscore the importance of negative reinforcement and stress models in understanding compulsive behaviour.

The current body of work should encourage the compulsivity research community to conduct further multidimensional research studies that combine various aspects of function in a multimodal way. We are convinced that this integrative approach could be the beginning of a new taxonomy for understanding compulsive behaviour and disentangle the mechanisms behind its psychopathology.

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Appendix 1

Table 1: Pearson correlation between Primary compulsion as measured by domain specific Y-BOCS and lower order constructs of Experiential Avoidance as measured by the MEAQ.

	Procrastination	Distraction Suppression	Repression Denial	Distress Endurance	Behavioural Avoidance	Distress Aversion
Compulsivity	.22	.094	.070	- .35*	.33*	.36*

* $p < .05$