Universidade do Minho
Escola de Medicina

Pedro Miguel Silva Moreira

The dynamics of decision making: An approach to distinct valuation systems

Cofinanciado por:

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The dynamics of decision making: An approach to distinct valuation systems

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Trabalho efetuado sob a orientação do
Professor Doutor Patrício Ricardo Soares Costa
e do
Professor Doutor Pedro Ricardo Luís Morgado

março de 2019

STATEMENT OF INTEGRITY

I hereby declare having conducted my thesis with integrity. I confirm that I have not used plagiarism or any form of falsification of results in the process of the thesis elaboration. I further declare that I have fully acknowledged the Code of Ethical Conduct of the University of Minho.

University of Minho. 04/03/2019

Full Name

PEDRO MIGUEL SILVA MOREIRA

Signature

“Many ideas happen to us. We have intuition, we have feeling, we have emotion, all of that happens, we don't decide to do it. We don't control it. (...) We think, each of us, that we're much more rational than we are. And we think that we make our decisions because we have good reasons to make them. Even when it's the other way around. We believe in the reasons, because we've already made the decision.”

“Friends are sometimes a big help when they share your feelings. In the context of decisions, the friends who will serve you best are those who understand your feelings but are not overly impressed by them.”

Daniel Kahneman

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The neural dynamics of decision-making: an approach to different valuation systems

Abstract

As human beings, we are constantly making decisions. Decision-making involves the ability of selecting among different alternatives to produce a given outcome. Due to the crucial relevance of decision-making in our everyday living, its study has been progressively established in the scientific literature. In addition, the study of the neurobiological mechanisms underlying these processes has been applied to some neuropsychiatric disorders, where the decision-making ability is compromised. One of such examples is the case of Obsessive-Compulsive Disorder (OCD) – a neuropsychiatric disorder characterized by the occurrence of obsessive thoughts and ritualistic actions intended to reduce the anxiety provoked by these thoughts. With the repetition of the cycle *obsessions – anxiety – compulsions – reduction of anxiety*, the compulsive behavior is progressively established as a natural rewarding trigger. As such, patients will engage in this habitual pattern of compulsive behaviors – even if they are no longer being rewarding for the subject. For these reasons, these patients are described as over-reliant on habits and having an impaired ability to shift from the habit-based to the goal-directed system of decision-making. These characteristics make these patients ideal candidates for the study of the neural processes involving a pathological form of decision-making.

In this work, we implemented a comprehensive approach for the characterization of decision-making processing in these patients. Using a multimodal neuroimaging approach, we observed that OCD patients are characterized by a variety of intrinsic structural and functional brain alterations, in comparison to healthy controls – involving networks of brain regions that seem to be relevant for emotional processing. Besides these findings, we observed significant differences on the association between the structure of brain regions that are consistently involved in decision-making processing and decision-making profiles in OCD. When assessed during monetary risky decision-making, compared with healthy individuals, these patients present a significantly reduced brain response in the regions of the occipital cortex and cingulate areas; furthermore, they also display altered task-dependent modulation of the activity of limbic regions. Likewise, OCD patients also had an altered modulation of the activity of the anterior cingulate and basal ganglia nuclei, when receiving negative outcomes (*i.e.,* when they perceive losses).

Considering these neurobiological dynamic alterations and that the disorder is known to be associated with an altered emotional processing, we hypothesized that there might be an underlying influence of emotional processing during decision-making in these patients. To address this, we implemented a meta-analytic investigation which revealed that the neurobiological mechanisms that are typically altered in emotional processing in these patients are preferentially associated with reward processing. Following-up on this notion, we proceeded to the characterization of how the emotional processing interferes with central and autonomic nervous systems in non-clinical samples. For this purpose, we implemented a complementary meta-analytic aggregation of the literature and by performing an empiric investigation where we studied the dynamic oscillations of the brain connectome during emotional induction. In addition, we addressed the relevance of emotional valence for impulsive behavior, from a psychometric perspective, and how affective dimensions of impulsive behavior are fingerprinted at central nervous system. Finally, we assessed whether the induction of an affective state influences goal-directed decision-making, with a focus on risky decision-making. Even though we find little evidence for the discrimination of individual emotional categories on psychophysiological responses, the salience of the emotional stimuli seems to be directly associated with the magnitude of these responses. On top of this, we found evidence for the impact of contrasting emotional valences on behavioral correlates. Altogether, these results point to the notion that emotion might have a non-straightforward, although crucial, modulatory influence on decision-making, mainly in neuropsychiatric contexts. Future research is needed to clarify the effectiveness of interventions focused on the emotional processing on the modulation of decision-making characteristics.

As dinâmicas da tomada de decisão: uma abordagem a diferentes sistemas de valoração

Resumo

O nosso quotidiano é constantemente caracterizado por situações que requerem que tomemos decisões. Estes processos envolvem a capacidade de selecionar entre diferentes alternativas para produzir um determinado resultado. Devido à relevância da tomada de decisão no nosso dia a dia, o estudo destes processos tem ganho uma ênfase progressiva na investigação científica. Adicionalmente, o estudo dos mecanismos neurobiológicos subjacentes a estes processos tem sido investigado no contexto de diversas doenças neuropsiquiátricas, nas quais a capacidade de tomada de decisão se encontra comprometida. A Perturbação Obsessivo-Compulsiva (POC) destaca-se como um exemplo de relevo neste âmbito. Esta patologia caracteriza-se pela ocorrência de pensamentos obsessivos e comportamentos ritualísticos que são desencadeados para reduzir a ansiedade provocada pelas obsessões. A contínua exposição ao ciclo *obsessões – ansiedade – compulsões – redução da ansiedade* leva a que as compulsões se estabeleçam progressivamente como recompensadores naturais. Desta forma, os pacientes tenderão a enveredar neste padrão de hábitos caracterizado por episódios de compulsividade, mesmo que estes deixem de proporcionar qualquer tipo de recompensa. Por estas razões, os doentes com POC são tipicamente descritos como indivíduos com uma dependência excessiva de hábitos e com uma disfunção na transição deste padrão comportamental para o sistema de tomada de decisão orientado para objetivos. Estas características levam a uma conceptualização dos doentes com POC como potenciais candidatos para o estudo dos processos de tomada de decisão, na sua forma patológica.

Neste trabalho, procedemos à implementação de uma abordagem compreensiva para a caracterização da tomada de decisão nestes doentes. Através de uma investigação de neuroimagem multimodal, observámos que, em comparação com indivíduos saudáveis, os doentes com POC apresentam uma diversidade de padrões cerebrais estruturais e funcionais alterados, envolvendo redes de regiões cerebrais tipicamente associadas com o processamento emocional. Foram ainda detetadas alterações significativas na associação entre a estrutura de regiões tradicionalmente implicadas nos processos de tomada de decisão e o perfil de tomada de decisão nestes doentes. Quando avaliados num paradigma de tomada de decisão económica, estes indivíduos demonstram uma magnitude de resposta neurobiológica reduzida em regiões

occipitais e do córtex cingulado e uma modulação da atividade de regiões límbicas na passagem de níveis mais elevados para níveis mais baixos de risco. Adicionalmente, os doentes com POC apresentam uma modulação alterada do córtex cingulado anterior e dos gânglios da base em resposta a resultados negativos (ou seja, quando se apercebem de uma perda monetária).

Atendendo às alterações das dinâmicas de resposta neurobiológica e ao facto de a doença ser caracterizada por um processamento emocional alterado, propusemos a hipótese de existir uma influência do processamento emocional na tomada de decisão nestes doentes. No sentido de explorar esta hipótese, realizámos uma investigação meta-analítica que evidenciou que os mecanismos neurobiológicos que se encontram alterados durante o processamento emocional nestes doentes estão preferencialmente associados ao processamento da recompensa. Assim, procedeu-se de seguida à caracterização de como o processamento emocional interfere com o sistema nervoso central e autónomo em populações não clínicas. Para este efeito, complementámos uma revisão sistemática da literatura com uma investigação empírica no sentido de estudar as dinâmicas de oscilação do conectoma cerebral humano durante a indução emocional. Abordámos ainda a relevância da valência emocional no comportamento impulsivo, à luz de uma abordagem psicométrica, e se existem assinaturas neurobiológicas de dimensões emocionais ao nível do sistema nervoso central. Finalmente, abordamos se a indução de estados emocionais contrastantes influencia de forma diferencial a tomada de decisão de risco. Apesar de termos detetado uma evidência reduzida no que respeita à discriminação de categorias emocionais individuais em correlatos psicofisiológicos, a saliência emocional dos estímulos parece estar diretamente associada a estas respostas. Mais ainda, obtivemos evidência para um impacto da indução de valências emocionais contrastantes em correlatos comportamentais. Globalmente, estes resultados sugerem que as emoções assumem um papel complexo, embora crucial, na modulação da tomada de decisão, particularmente em contextos neuropsiquiátricos. Investigações futuras poderão clarificar a eficácia de intervenções focadas no processamento emocional na modulação das características da tomada de decisão.

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List of Abbreviations

A

AAL - Automated Anatomic Labelling

ACC - Anterior Cingulate Cortex

ADHD – Attention-Deficit Hiperactivity Disorder

ANOVA - Analysis of Variance

ANS - Autonomic Nervous System

B

BART - Balloon Analogue Risk Task

BF – Bayes Factor

BFC – Bold Phase Coherence

BG - Basal Ganglia

BOLD - Blood Oxygenation Dependent Level

BP - Blood Pressure

BPM - Breaths Per Minute

C

CFA - Confirmatory Factor Analysis

CNS - Central Nervous System

CSF - Cerebrospinal Fluid

CTSC - Cortico-Striato-Thalamo-Cortical

D

dFC - Dynamic Functional Connectivity

DAN – Dorsal Attention Network

DMN - Default Mode Network

dlPFC – Dorsolateral Prefrontal Cortex

DSM - Diagnostic and Statistical Manual of Mental Disorders

DTI - Diffusion Tensor Imaging

DWI – Diffusion-Weighted Imaging

E

EDA - Electrodermal activity

EFA - Exploratory Factor Analysis

EEG - Electroencephalography

EGA - Exploratory Graph Analysis

EMG - Electromiography

EPI - Echo Planar Imaging

F

FC - Functional Connectivity

FDR - False-Discovery Rate

fMRI - Functional Magnetic Resonance Imaging

FoV - Field of View

FSL - FMRIB Software Library

FWE - Family Wise Error

FWHM - Full Width Half Maximum

G

GLM - General Linear Model

GM - Grey Matter

GMV – Grey Matter Volume

H

HAM-A - Hamilton Anxiety Rating Scale

HAM-D - Hamilton Depression Rating Scale

HC - Healthy Controls

HPA - Hypothalamic-Pituitary-Adrenal

HR - Heart Rate

HRF - Hemodynamic Response Function

HRV - Heart Rate Variability

HVN - High Visual Network

I

ICA- Independent Component Analysis -

IOG - Inferior Occipital Gyrus

L

LEiDA - Leading Eigenvector Analysis

M

MACM - Meta-Analytic Connectivity Modelling

MEG - Magnetoencephalography

MNI - Montreal Neurological Institute

mOFC – Medial Orbitofrontal Cortex

MPRAGE - Magnetization Prepared Rapid Gradient Echo

MRI - Magnetic Resonance Imaging

MTG - Middle Temporal Gyrus

N

NAcc - Nucleus Accumbens

NBS - Network Based Statistics

O

OCD - Obsessive-Compulsive Disorder

OCI-R - Obsessive-Compulsive Inventory

OFC - Orbitofrontal Cortex

P

PANAS - Positive and Negative Affect Scale

PD – Prisoner's Dilemma

PET - Positron-Emission Tomography

PFC - Pre-Frontal Cortex

PNS - Peripheral Nervous System

PPG - Photoplethysmogram

PVN - Primary Visual Network

R

ROI - Region of Interest

RR - Respiratory Rate

rs-FC - Resting-Sate Functonal Connectivity

rs-fMRI - Resting-State Functional Magnetic Resonance Imaging

RSA - Respiratory sinus arrhythmia

RSN - Resting-State Networks

S

SAM - Self Assessment Manikin

SC - Skin Conductance

SCL - Skin Conductance Level

SCR - Skin Conductance Response

SMN - Sensorimotor Network

sMRI - Structural Magnetic Resonance Imaging

SPSS - Statistical Package for Social Sciences

SSRI - Selective Serotonin Reuptake Inhibitors

T

TBSS - Tract Based Spatial Statistics

TCA - Tricyclic Antidepressants

TFCE - Threshold-Free Cluster Enhancement

TE - Time to Echo

TG – Trust Game

TR - Time to Repetition

U

UG - Ultimatum Game

UPPS-P - Urgency, Premeditation, Perseverance, Sensation Seeking

V

VAN - Ventral Attention Network

VBM - Voxel Based Morphometry

vlPFC – Ventrolateral Prefrontal Cortex

vmPFC – Ventromedial Prefrontal Cortex

W

WM - White Matter

Y

Y-BOCS - Yale-Brown Obsessive-Compulsive Scale

Introduction

In our everyday lives, we are constantly dealing with situations that require an ability to make decisions effectively. Examples of these situations include very ordinary decisions, such as deciding what to wear in the morning, what to order in a restaurant, to more sporadic scenarios, including whether to invest in the stock market, to buy a new car or a house, or choosing between political candidates for the national elections. In all these cases, an individual selects a specific action among a set of alternatives to produce a specific outcome. The end result will have an impact on the psychological state of the decision-maker (Paulus, 2007).

There has always been a great interest in understanding how we make decisions and how they are modulated, which has positioned the science of decision-making as a hot topic of research for several decades. Two main approaches have dominated the study of decision-making: the first – the normative decision theory – conceptualizes the process of decision-making as the search for the optimal choice for a given scenario (Morgenstern & Von Neumann, 1953); the second – the descriptive decision theory – aims to identify a set of principles that can parsimoniously account for the actual choices of humans and animals (Lee, 2013).

Historically, decision-making models were originally concerned about predicting future choices/outcomes, rather than studying the neurobiological mechanisms governing such processes (Johnson & Ratcliff, 2014). With cumulative knowledge regarding the functioning of the brain associated with the output of simple decisions, such as the role of the medial orbitofrontal cortex (mOFC) or the ventral striatum, this trend started to change. This emerging field – commonly recognized as neuroeconomics – aims to understand the neural mechanisms underlying decision-making. For this purpose, researchers in this field need to understand the complexity of decision-making, including systematic biases, irrational, or inelegant patterns of choice (Santos & Platt, 2014), which are guided by representations of gains, losses and probabilities (Kahneman & Tversky, 2013).

Based on existing theoretical models of decision-making in the fields of economics, psychology and computer science, Rangel, Camerer and Montague (2008) proposed a computational framework for conceptualizing decision-making. According to the authors, the act of decision-making involves a set of critical phases: representation, valuation, action selection, outcome evaluation and learning. The first process – the **representation** phase – consists on the representation of the set of alternatives for a given decision-making scenario, as well as the

internal and external states relevant for those valuations. This process is of upmost importance for the identification of the potential sources of action to be evaluated.

Based on the set of available alternatives, the individual then assigns a value to each action – the **valuation** phase. The scientific literature supports the existent of multiple valuation systems: *Pavlovian*, *habitual* and *goal-directed* systems. The *Pavlovian* system is characterized by an assignment of values to evolutionarily adequate responses (including preparatory behaviors and responses to reward). This valuation system encompasses a small set of innate behaviors, whose computational and neurobiological characterization is not well understood. The second system – the *habitual* system – enables the individual to assign values to an extensive amount of actions. Habits are implemented throughout stimulus-response (S-R) associations, which are formed based on repeated trial and error processes, generated in stable environments. The last valuation system – the *goal-directed* system – is established throughout stimulus-outcome-response (S-O-R) associations. In contrast with the habitual system, the goal-directed system allows the updating of the value the action, when the value of the outcome associated with that action changes. As such, whereas the goal-directed system is determinant for the formation of recompensing associations, the habitual system relies on the maintenance of these learned associations (Aarts & Dijksterhuis, 2000). The goal-directed system plays a crucial role to face the ever-changing environment – allowing us to learn to select among alternative actions, based on their consequences (*e.g.,* when we first select the best route to drive from home to work), however it demands an effortful cognitive control. To increase the efficiency, it is appropriate to automatize recurring decision processes as habits where we no longer need to evaluate their consequences (*e.g.,* after driving to work for some time in the established route, we automatically follow that route) (Soares et al., 2012). Thus, the ability to shift between habit-based and goal-directed actions is a condition for appropriate decision-making (Balleine, Delgado, & Hikosaka, 2007).

The valuation of the different alternatives will enable the comparison between each option and will guide the choice of an alternative – **action selection**. It has been suggested that the brain assigns control to the system with the less uncertain estimate of the true value of actions. Thus, with repeated experience the accuracy of the estimates produced by the habitual system will increase, meaning that this system is more likely to govern behavior. As such, whereas under constantly changing and unstable environments, it is optimal to assign the control

to the goal-directed system, in familiar, controlled and stable environments, it is more efficient to rely on the habitual system.

Finally, the individual will evaluate the consequences of the action by assessing the desirability of the outcome generated by previous decisions – the **outcome evaluation** phase. It has been demonstrated that the activity of the mOFC plays a crucial at this phase, being associated with the subjective reports during the experience of a reward. On the opposite, the activity of the insula and anterior cingulate cortex (ACC) has been described to accompany the experience of negative outcomes. Furthermore, the state-of-the-art have been suggesting that the outcome evaluation – as expressed by the modulation of the mOFC – is influenced by prior expectations and beliefs.

Most decisions involve some form of learning. For an individual to make good decisions, he/she needs to learn from previous experience which are the actions that conduct to the desired reward. Thus, the outcome evaluation from previous experiences will be used for updating the other steps of the decision-making process so that the quality of future decisions can be improved – the **learning phase**. For this to happen, the brain must implement a set of computations, including representing the most convenient alternative to a given scenario, assignment of action values based on the anticipated outcomes and selection of action to the most appropriate valuation system.

An overview of neurobiological systems and their relevance for decision-making

The central nervous system

Several modalities are available for studying the human brain. Nonetheless, in the last decades, MRI has been established as the tool of preference for the assessment of brain structure and function, overtaking other popular modalities such as electroencephalography (EEG), positron-emission tomography (PET) or magnetoencephalography (MEG) (Van Horn & Poldrack, 2009). MRI can provide a detailed anatomical characterization of gray and white-matter structures with an excellent spatial resolution (1 mm^3 or below). This information can be used to

compare structural differences (*e.g.,* brain volume, cortical thickness, curvature) between populations or to assess the association between brain structure and individual traits. In addition, MRI information is also widely used for studying the function of the brain, by characterizing the blood oxygen level dependent (BOLD) response, which reflects alterations in deoxygenated hemoglobin (or deoxyhemoglobin; which acts as a paramagnetic agent detected with MRI) in response to the presentation of a stimulus (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Raichle et al., 2001; Uludağ, Müller-Bierl, & Uğurbil, 2009). In addition to task-related brain activity, there are also spontaneous brain fluctuations even when individuals are at rest, in which networks of correlated temporal patterns are identified (Smith et al., 2009). These patterns are thought to reflect the state of the human brain in the absence of goal-directed neuronal action and external input (Gusnard & Raichle, 2001) and have been extensively replicated across populations (Damoiseaux et al., 2006).

Even though most studies have characterized the correlates of decision-making at the functional level, *i.e.,* by approaching the variations of the BOLD signal during decision-making paradigms, it is also possible to assess the association between intrinsic brain patterns (either structural or task-independent functional patterns) and decision-making behavior. While the former strategy has the advantage of accounting for the dynamic variation of brain activity with the contingencies of the experimental paradigm, it may be affected by characteristics, such as effort or attention.

The autonomic nervous system

The electrodermal and cardiovascular systems have been widely used to characterize the role of the autonomic nervous system in the decision science field. With regards to the former system, whereas the skin plays a critical role on the maintenance of water balance and of constant core body temperature through the variation in the production of sweat (Dawson, Schell, & Filion, 2007), the activity of its eccrine glands has been demonstrated to be particularly relevant for psychologically relevant stimuli in scientific experiments (Grice & Segre, 2011). In a similar fashion, heart rate variations have been associated with the preparation for aversive events (Somsen, Van der Molen, & Orlebeke, 1983).

When we engage with surrounding stimuli, we experience a particular state of body and mind, manifested by physiological arousal and reactivity (Critchley, Eccles, & Garfinkel, 2013). While there is no general consensus regarding the exact role of physiological arousal on the modulation of decision-making behavior, it is widely recognized that the activation of the sympathetic nervous system is of upmost relevance for gambling behavior (Agren, Millroth, Andersson, Ridzén, & Björkstrand, 2019). As a matter of fact, it has been reported that physiological arousal is associated with the risk-level in gambling tasks both in healthy (Crone, Somsen, Beek, & Van Der Molen, 2004) and in pathological conditions (Bechara, Damasio, Damasio, & Anderson, 1994; Bechara & Damasio, 2002). For instance, heart rate (HR) decelerations, increased skin conductance level (SCL) (Crone et al., 2004) or elevated skin conductance responses (SCR) (Bechara, Damasio, & Damasio, 2000) have been associated with risk-taking behavior and with decision-making under ambiguity (FeldmanHall, Glimcher, Baker, & Phelps, 2016).

The interplay between emotion and decision-making processing

From a psychological perspective, when dealing with the feedback of a decision, the individual compares the obtained outcomes of a decision against beliefs regarding their likelihood. As such, it is proposed that both experienced and anticipated emotions are important modulators of the decision-making process (Crone et al., 2004). This notion has been comprehensively explored in the affective neuroscience literature, where it has been proposed that emotion plays a crucial role in decision-making processing, namely on the representation of value (Phelps, Lempert, & Sokol-Hessner, 2014).

The link between emotional processing and decision-making ability can be traced back to the famous case of Phineas Gage. After being involved in a bizarre accident, where a tamping iron was hurled through Gage's brain – damaging his ventromedial prefrontal cortex (vmPFC) – he immediately recovered full consciousness and ability to speak and even walk with the help of his co-workers. Even though his intelligence, movement or speech remained intact, Gage survived as a different man – "Gage was no longer Gage", in the words of his friends. Above all,

Gage became an irresponsible and irreverent person, without sense of compromise or respect for social norms. In addition, his ability to make rational decisions in personal and social matters was severely compromised, as well as his emotional responses (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Further research demonstrated that patients with impairments in emotional processing, following lesions to the vmPFC, displayed altered decision-making in gambling tasks (Bechara, 2004; Bechara et al., 2000).

Impulsivity, compulsivity and decision-making

The multi-dimensional nature of impulsivity and its relationship with decision-making

Classical definitions of impulsivity emphasize aspects related with impaired cognitive control, inadequate sampling of sensory evidence (defined as reflection impulsivity), failures in motor inhibition, tendency to achieve immediate smaller rewards (over delayed larger rewards) and risk-taking behavior (Dalley, Everitt, & Robbins, 2011; Evenden, 1999). Impulsive behavior constitutes a multi-faceted set of constructs with a crucial role on decision-making processes (Dalley et al., 2011). This is corroborated by the fact that pathological levels of impulsivity – as those manifested in conditions such as attention deficit hyperactivity disorder (ADHD) (Garon, Moore, & Waschbusch, 2006), substance addiction (Grant, Contoreggi, & London, 2000), antisocial personality disorder (APD) (Mazas, Finn, & Steinmetz, 2000) or pathological gambling (Brand et al., 2005) – are characterized by impaired decision-making abilities.

Even though most approaches focus on the sensorimotor or cognitive aspects of impulsive behavior, recent contributions conceptualize emotion-based rash actions as a key form of impulsivity (Cyders et al., 2007). This complements the classical views of impulsivity, highlighting the relevance of emotional drivers on the manifestation of impulsive behavior. In fact, it has been hypothesized that extreme mood states (either positive or negative) can have an impact on risky decision-making and that urgency has a different role from that of other forms of impulsivity in the explanation of risk-taking (Cyders et al., 2007). Altogether, this raises the notion that different traits of impulsivity explain different types of risky decision-making and that

mood-based impulsivity suppress other forms of impulsivity in the explanation of mood-based risk-taking and in identifying individuals at risk for pathological gambling.

OCD as a decision-making disorder

An important lesson from the Gage's case pertains to the impact of decision-making impairments on several aspects of our daily life. These impairments seem to be a key feature of conditions associated with compulsivity – such as obsessive-compulsive disorder (OCD) – which is commonly acknowledged as particularly striking example of impaired decision-making ability.

It has been proposed that OCD is a prototypic condition, resulting from dysfunctions in decision-making (Nestadt et al., 2016). These individuals are characterized by a reliance on repetitive behaviors which allows them to reduce the extreme levels of anxiety provoked by obsessive thoughts – *i.e.,* compulsive behaviors function as the response that will trigger the reward (end of the unwanted state). As such, these repetitive behaviors will be progressively established as the prototypical response to unwanted stimuli. Consequently, this over-reliance on habitual behaviors will preclude a proper shift towards more rewarding strategies. In addition to these reasons, as previously mentioned, there is a large interplay between emotional processing and decision-making behavior. Given that OCD patients tend to display a heightened perception of threat and an exaggerated evaluation of the likelihood of negative outcomes (Sookman & Pinard, 2002), they typically demonstrate an avoidance behavior towards even the slightest risk (Admon et al., 2012; Frost, Steketee, Cohn, & Griess, 1994). This picture raises the possibility that OCD patients are good candidates for the study of abnormal decision-making.

Even though substantial progress has been achieved regarding the neurobiological bases of psychiatric disorders – such as OCD – there are still many open questions for further investigation (Lee, 2013). In particular, a greater understanding of the neural bases of decision-making may dramatically impact the diagnosis and treatment of OCD as well as other neuropsychiatric disorders (Lee, 2013; Maia & Frank, 2011).

Objectives

In this project, we aimed to extend the current knowledge of the underlying processes of decision-making, by combining the study of neural and behavioral mechanisms. At the behavioral level, we approached decision-making by evaluating different valuation systems (*i.e.*, habitual and goal-directed) as well as different modulators of goal-directed decisions. The neural mechanisms of these processes were comprehensively explored by conducting a multimodal investigation. Also, we explored how the dynamics of different decision-making domains are affected by the influence of contextual conditions, focusing on the impact of emotional induction. One of the goals of the project relied on the identification of potential therapeutic targets for neuropsychiatric disorders characterized by marked impairments of decision-making. In this context, we focused on OCD as a condition markedly characterized by deficits in decision-making processing.

For this project, we defined the following aims:

- to investigate the neural patterns of distinct valuations systems of decision-making across healthy individuals;
- to characterize the neurobiological patterns of OCD – which is here used as a proxy for the study of impaired decision-making processing;
- to compare decision-making processing behavior of OCD with healthy individuals and their relationship with neurobiological markers;
- to understand the role of emotion-related processing for the pathophysiology of OCD and how this may contribute for decision-making impairments;
- to address the impact of emotion processing on central and peripheral measures of the nervous system:
- to explore the neurobiological correlates of impulsivity, namely emotion-related impulsivity and how they are associated with decision-making behavior;
- to assess the impact of emotional processing on behavioral correlates of decision-making.

Chapters' overview

This thesis is organized in five main chapters. **Chapter 1** provides a comprehensive review of the neuroimaging literature of the neurobiological correlates of decision-making.

Chapter 2 is focused on the characterization of OCD as a potential candidate of pathological decision-making ability, throughout the characterization of structural and resting-state functional connectivity (FC) patterns of OCD (Chapters 2.1 and 2.2), by establishing the link between intrinsic brain patterns and behavioral profiles of risky decision-making behavior in OCD (Chapter 2.3). We also assess the patterns of neural activation during the anticipation and feedback to decision making of varying risk levels (Chapter 2.4) In the last section of the second chapter, we provide meta-analytic evidence for the relationship between emotional processing in OCD patients and reward processing (Chapter 2.5).

On **Chapter 3**, we present a comprehensive characterization of the impact of emotional induction on the autonomic (Chapter 3.1) and central nervous system, where we characterize dynamic Functional Connectivity (dFC) states associated with the induction of contrasting affective valence (Chapter 3.2).

On **Chapter 4**, we explore the association between emotional processing and decision-making. For this purpose, we approach the psychometric properties of impulsivity and how it is associated with psychophysiological patterns (Chapter 4.1). Finally, we developed the experimental protocol to study the impact of the induction of affective states of contrasting hedonic valence on the behavioral responses to decision-making involving risk (Chapter 4.2).

In the last section of this thesis, **Chapter 5**, we provide an integrative discussion of the findings reported across the different chapters, discussing the main strengths and limitations of this work a whole, and suggests directions for future research. The organization of the main themes of the thesis is summarized on Fig. 1.

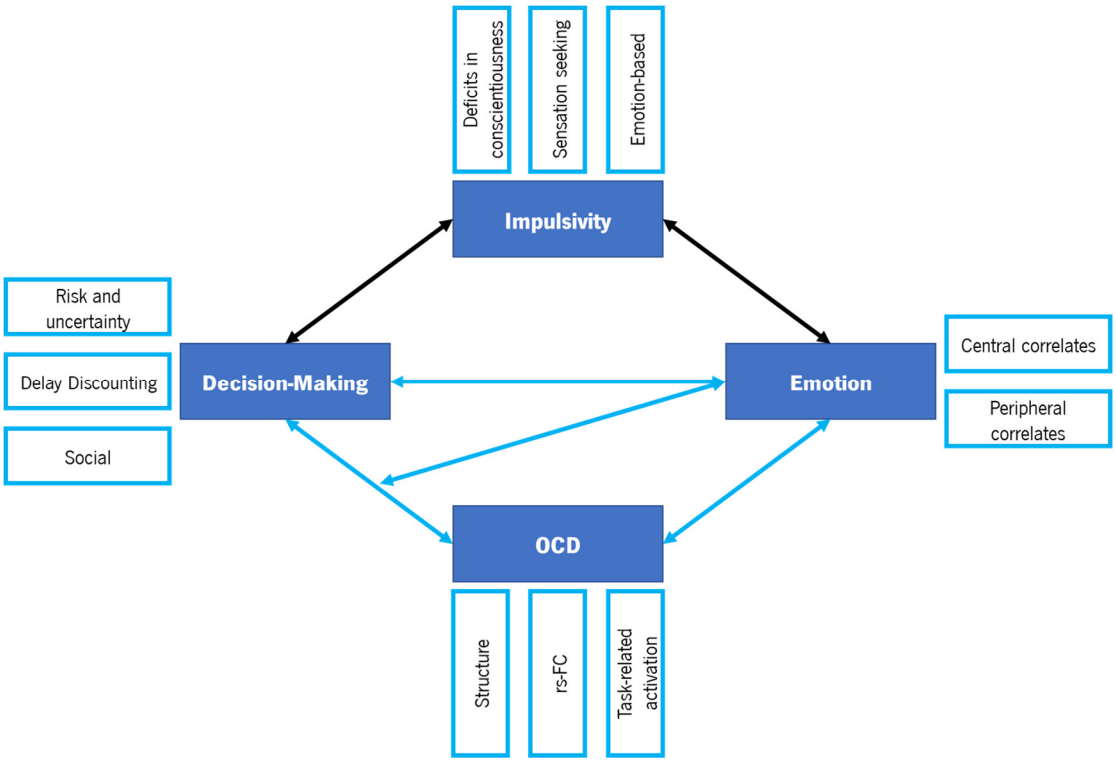

Fig. 1. Overview of the organization of the main themes of the thesis. Black arrows refer to previously reported relationships between the constructs. Arrows and squares in light blue indicate the topics that are tackled in this thesis.

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Chapter 1. The neurobiological mechanisms of decision-making

CHAPTER 1.1

A threat to reason? A meta-analysis of the neural mechanisms of decision-making

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Manuscript in preparation

A threat to reason? A meta-analysis of the neural mechanisms of decision-making

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Keywords: decision-making, risk and uncertainty, delay discounting, ultimatum game, trust game, reciprocity, norm compliance, fMRI, meta-analysis

Abstract

Traditional models describing the process of decision-making are typically influenced by an economic account to explain human decisions. In line with this perspective, humans decide in accordance with the maximum expected utility*, i.e.,* aiming to maximize their gains. Accumulative evidence of scientific research has critically challenged this view, by demonstrating that we, as humans, do not make our decisions from a pure rational perspective. In this work, we intended to consolidate the last decades of scientific research examining the neurobiological correlates associated with different value modulators of goal-directed decision-making. We aggregated the data from neuroimaging studies assessing human decision-making under risk and uncertainty, temporal discounting and social decision-making. Using an activation likelihood estimation approach, we identified patterns of consistent brain activation across studies. Consistent patterns of brain activation were observed for the right insula for risk and uncertainty, norm compliance and reciprocity. On the other hand, choosing delayed rewards was associated with consistent brain activation in frontal, parietal and cingulate regions. Together, these results provide a comprehensive summary of decision-making processing, constituting a unique combination of neuroimaging findings associated with the different value modulators of decision-making.

Highlights

- Humans frequently decide in an unpredictable and inconsistent fashion;

- Decision-making behavior is modulated by several variables, including risk, time or social modulators;

- We report the results of a coordinate-based meta-analytic aggregation of 84 studies exploring the brain correlates of different modulators of goal-directed decision-making;

- There is a considerable overlap between the meta-analytic maps associated with these value modulators.

1. Introduction

Our everyday living is marked by a variety of aspects that require an ability to make effective decisions, including very basic decisions, such as choosing what to wear or what to eat, and more complex decisions, such as deciding to get married or buying a new car. According to traditional economic theories, a decision is made based on the maximum expected utility – which is acknowledged as the normative model of rational choice (Keeney & Raiffa, 1993). However, the study of decision-making is a challenging topic, given that the future consequences from an action are rarely predictable (Kahneman & Tversky, 2013). This uncertainty influences individuals' choice, which makes these decisions frequently sudden and inconsistent in their nature (Wu, Sacchet, & Knutson, 2012). Thus, due to the relevance of decision-making, it is of upmost relevance to understand the processes underlying the normal and abnormal ability to make decisions.

The study of decision-making processes has been recognized as a relevant tool for better understanding a multitude of behavioral and mental disorders characterized by a disturbed decision-making ability. Consequently, an extensive body of scientific research, referred as decision neuroscience, has been trying to unravel the neural mechanisms underlying specific decision-making processes. The increasing number of publications on this topic has been contributing to advances in the knowledge of the neurobiology of decision-making. Several conditions, such as depression (Yang et al., 2014), substance abuse, pathological gambling (Yan et al., 2014), eating disorders (Chan et al., 2014) and obsessive-compulsive disorder (Sachdev & Malhi, 2005) have been characterized by altered decision-making patterns.

Decision-making is thought to be dependent on the interplay between multiple processes, including the value representation, action valuation, response selection, learning and socio-emotional processing (Blakemore & Robbins, 2012; Rangel, Camerer, & Montague, 2008) (Figure 1). When deciding between options, individuals can rely on two different systems. The first system (the habit system) is established through trial-and-error: by being repeatedly exposed to a given contingency, *i.e.,* stimulus-response associations), subjects learn to assign value to stimulus-outcomes associations (Rangel et al., 2008) and the action with the largest learned value will be taken and generalized for the assigning of values in future choices (Rangel & Hare, 2010). The second system (the goal-directed system) is implemented by action-outcome associations. It governs our decisions when we are exposed to new, unfamiliar, scenarios and

updates the value of an action when the outcomes associated with that action change (Rangel et al., 2008). At the neurobiological level, the dorsal striatum is thought to be a critical player on the modulation of these systems. Two functional circuits underlying these systems have been described: one involving the dorsolateral striatum and mediates habits' learning; the second involving the dorsomedial striatum mediates the learning of action-outcomes (Balleine, 2005). In addition, the orbitofrontal cortex (OFC) (Hare, O'Doherty, Camerer, Schultz, & Rangel, 2008) and interactions between the dorsolateral prefrontal cortex (dlPFC) and ventromedial prefrontal cortex (vmPFC) are thought to underline the encoding of outcome-value associations (Rudorf & Hare, 2014)

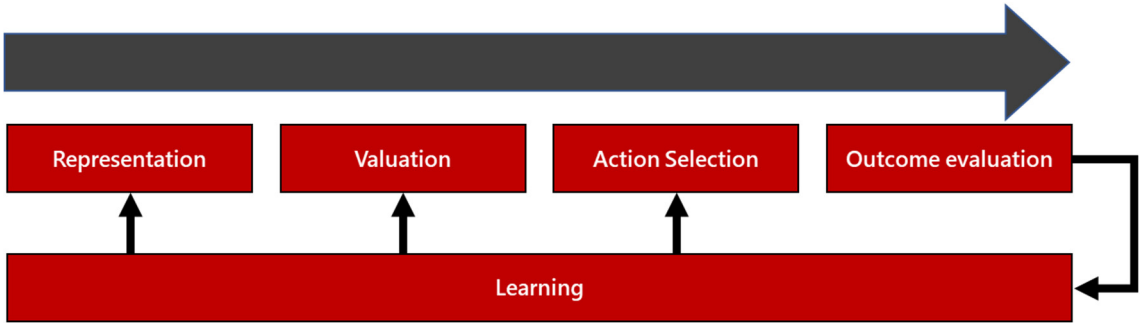

Figure 1. Representation of the different phases of decision-making processing. The individual first represents the set of alternatives for a given decision-making scenario (the representation phase and assigns a value to each action (the valuation phase), which will guide the choice of an alternative (action selection). Finally, the individual will evaluate the consequences of the action by assessing the outcome (outcome evaluation phase) which will be used for updating the representation, valuation and action selection of decision-making scenarios (learning phase). Scheme adapted from Rangel et al (2008).

In this integrative review, we aim to provide a further elaboration on the modulators of goal-directed decision-making. Below, we provide a comprehensive characterization of these value modulators, with an emphasis on the experimental approaches that are used to tackle each modulator. We also summarize the theoretical models on this topic and provide a description of different psychological conditions characterized by consistent alterations in different decision-making scenarios.

1.1. The modulators of goal-directed decision-making

1.1.1. Risk and uncertainty

All decisions involve some degree of risk, given that action-outcome associations are probabilistic. To make good decisions, the goal-directed system needs to take into account the likelihood of the different outcomes (Rangel et al., 2008). In this scenario, most risky choices require an individual to consider uncertainty associated with potential gains and losses (Wu et al., 2012). This modulator of decision-making has been emphasized in science fiction productions – such as the Matrix – which is described in a great review of the neuroeconomics literature (Knutson & Huettel, 2015). The authors detail a scene from the movie where Neo is offered by Morpheus with an irrevocable choice between two alternatives: one option (the blue pill) leads to the end of the story – where Neo will remain in the reality of the Matrix – an illusory world where humans are prevented from discovering that they are slaves to an external influence; the other option (the red pill) is to stay in Wonderland – where he would be able to find out what Matrix really is and what the machines are doing. In this example, the blue pill would correspond to the safe choice of keeping the ignorance of the world, whereas the red pill would unveil the unknown reality whereas exposing Neo with potential losses. People are described to be unequally sensitive to loses and winnings: typically, individuals are more sensitive to the possibility of losing than to the possibility of gaining (Novemsky & Kahneman, 2005). This scenario mimics typical experimental decision-making scenarios assessing risk-taking behavior, where individuals are usually presented with different options: one "safe" option, which is associated with a high probability of small gains, is contrasted with a "dangerous" option (or gamble), which is associated with a small probability of gaining a lot and a high probability of losing the bet. We, as humans, have a well described preference for right-skewed gambles, *i.e.,* we tend to choose gambles with very low-chances of winning a lot. In a seminal work by the famous behavioral economists Daniel Kahneman and Amos Tversky (2013), the authors proposed that the reasons underlying this right-skewed preferences rely on the fact that people have a bias towards an overweighting of small probabilities.

Imagine the following scenario: you are given the option to choose between a sure winning of 10.000€ and a 50% change of winning 30.000€. From the perspective of the maximization of utility, people would choose the second option as this would constitute the alternative giving the largest expected value ($EV_{optionA}$=10.000€*1=10.000€; $EV_{optionB}$=30.000€*0.5=15.000€). However, the state-of-the-art on this topic is consistent in

demonstrating that people tend to exhibit a preference for the sure option. In fact, individuals seem to be driven by the experience of positive arousal, with increased brain activity in circuits associated with gain anticipation, such as the nucleus accumbens (Wu, Bossaerts, & Knutson, 2011); whereas potential losses typically elicit risk-aversion choices, dependent on the activity of the anterior insula (Kuhnen & Knutson, 2005).

Rats with lesions of the nucleus accumbens core exhibited an increased risk-aversion, by choosing a larger, but uncertain, reward less often than control animals (Cardinal & Howes, 2005). Previous aggregations of neuroimaging studies have identified consistent patterns of brain activations during reward-based decision-making. In particular, regions such as the anterior insula, dorsomedial prefrontal cortex, thalamus, ventromedial prefrontal cortex and the ventral striatum were associated with the subjective value of choice alternatives (Bartra, McGuire, & Kable, 2013). Dorsal and ventral striatum, thalamus, orbitofrontal cortex, anterior insula, cingulate cortex (anterior and posterior divisions) and prefrontal cortex were found to consistently underlie the processing of reward-related decision-making (Liu, Hairston, Schrier, & Fan, 2011).

1.1.2. Delay discounting

Among the scientific literature, delay is widely recognized as one key determinant of the human behavior with a strong influence on individuals' actions (Lattal, 2010). When given the option of receiving something now or later, most of us would preferentially choose the immediate option. This is essentially due to the fact that having to wait for a reward reduces the subjective value associated with that option (Massar, Libedinsky, Weiyan, Huettel, & Chee, 2015). A decision increases in complexity when we have a conflict between the delay to reward and the magnitude of that same reward (Odum, 2011). In Aesop's fable "The Ant and the Grasshopper", the grasshopper spends the entire summer singing while the ant keeps working to save food for the winter time. When the winter comes, the starving grasshopper asks the ant for food. The ant declines the request and tell the grasshopper to dance the winter away now. The moral at the end focuses on the advantages of hard work over the dangerous of improvidence – as it highlights the relevance of being able to favor options that will result in advantageous outcomes in the future. Often, individuals prefer immediate rewards with smaller magnitudes in contrast with larger rewards delivered with delay. This phenomenon – referred as delay discounting (DD) – underlines an increased preference for immediate rewards with smaller outcomes over delayed

rewards with larger outcomes (Bickel & Marsch, 2001). An explanation of this phenomenon is likely to be related with the fact that an action with smaller reward in shorter time allows an earlier transition to the next action (Doya, 2008).

In DD paradigms, subjects are typically asked to make choices between successive hypothetical options, in which the amount of the immediate option decreases across trials as a function of *a priori* contingencies of the experimental task, or as a function on the subjects' response profiles. Whereas the tendency to DD is normally present across individuals, a sharp sensitivity to this phenomenon is associated with impulsive behavior (Steward et al., 2017) and characterizes a number of pathological conditions, such as attention-deficit/hyperactivity disorder (ADHD) (Jackson & MacKillop, 2016), schizophrenia (Brown, Hart, Snapper, Roffman, & Perlis, 2018), depression and borderline personality disorder (Story, Moutoussis, & Dolan, 2016), eating disorders (Decker, Figner, & Steinglass, 2015), addiction (Havranek et al., 2017), among others.

Evidence from animal models suggests that the serotonergic system plays a crucial role on impulsive behavior, namely in choices of larger but delayed rewards (Doya, 2008). An aggregation of neuroimaging studies reported that DD studies is associated with consistent patterns of brain activity in clusters located in several basal ganglia nuclei, temporal regions, insula, inferior and middle frontal cortex, parietal cortex and cingulate regions (Wesley & Bickel, 2014).

1.1.3. Social modulators: fairness and reciprocity

The study of social decision-making is usually framed in the context of game theory – which refers to the search for strategies that enable individuals to converge so that they can maximize their outcomes (Von Neumann & Morgenstern, 2007). Within the scope of this theory, Nash equilibrium is acknowledged as the set of strategies from which no single player can increase their payoff by changing his/her strategy unilaterally (Nash, 1950). Even though the Nash equilibrium provides a rationale perspective to social decision-making, a large body of evidence has consistently demonstrated that this assumption is violated in games involving cooperation and/or competition (Lee, 2008). Traditional perspectives are characterized by an

over-simplified assumption stating that human beings' decisions are characterized as exclusively self-regards (Fehr & Camerer, 2007).

In real-life situations, trust is a crucial element to almost every transaction (Berg, Dickhaut, & McCabe, 1995). Economic games are a powerful approach to investigate individuals' appraisals in social decision-making (Bellucci, Feng, Camilleri, Eickhoff, & Krueger, 2018). A behavioral paradigm, known as the *trust game* (TG), is implemented to mimic such situations, by assessing the reciprocity norm. In this game, two players – the investor (I) and the trustee (T) are involved. I is given an amount of money, from which he/she has to pass a proportion to T. The amount proposed by I is then doubled or tripled according to the experimental contingencies. Experiments with this paradigm highlight that Is typically invest more than half of their initial endowment (Camerer, 2003). However, if I predicts that T will not reciprocate, he/she will reduce their investment considerably (Aimone & Houser, 2012). In a similar fashion, Ts typically behave reciprocally to I, as the consciousness of having more money than the counterpart will evoke negative feelings (Chang, Smith, Dufwenberg, & Sanfey, 2011).

Another well-known paradigm to assess cooperative behavior is the *ultimatum game* (UG) (Güth, Schmittberger, & Schwarze, 1982). In this game, one player (the "proposer", P) is given a specific amount of money (*e.g.,* 10€) and asked to give a part of the total amount to a second player (the "responder", R). R may either accept or reject the offer. If R accepts the offer, the money is divided according to the offer between P and R; otherwise, none of the players receives anything. According to the predictions from game theory, players should make their decisions according to the maximization of their own gains. As such, P should offer R a token payment and R should accept any non-null offer (Kahneman, Knetsch, & Thaler, 1986). Decades of scientific research using this task demonstrate that, whereas there is a cultural variation in small-scale societies (Henrich et al., 2001), Ps typically make offers with an average of around 40% of the total amount of money (Henrich et al., 2005; Oosterbeek, Sloof, & Van De Kuilen, 2004). On the other side, Rs tend to reject offers below 20-30% of the total amount (Schuster, 2017). This norm violation elicits a negative emotional response in R, which is manifested in behavioral and neurobiological correlates (Pillutla & Murnighan, 1996; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003). The Fehr-Schmidt inequality aversion model attempts to explain such behavior, by proposing that individuals rely on a utility function, which expresses preferences for equality. According to this view, the choice of not accepting the unfair offer reflects a punishment

towards P in response to perceived unfairness, by enforcing the fairness norm (Fehr & Gächter, 2002; Fehr & Schmidt, 1999). These findings highlight that Nash equilibrium has a poor fit on the explanation of the dynamics of cooperation during UG and related bargaining games (Rubinstein, 1982). Altogether, these findings have supported the view that humans and other animals do not only decide based on their own self-interests; rather, individuals are particularly sensitive to injustice (Stallen et al., 2018) and consider the welfare of others during their social decisions (Fehr & Fischbacher, 2003; Lee, 2008).

In a variant of the UG, the *dictator game* (DG) (Kahneman et al., 1986), subjects are presented with similar offers. However, in this case individuals do not have the chance of rejecting the offer. When acting as the Ps on the DG, individuals typically offer less than in the UG – however, they still offer more than what would be predicted by a purely self-interest model (Kahneman et al., 1986; Proctor, Williamson, de Waal, & Brosnan, 2013). The *Prisoner's Dilemma* (PD) has an experimental apparatus with the main general principles, *i.e.,* players can either cooperate or maximize their own gains while prejudicing the other. Two players attempt to maximize their profit while predicting the opponent's imminent behavior. In the PD, a player would benefit by defecting irrespective of the other's move.

Social decision-making seems to be influenced by serotonin function. Experimental reduction of serotonin levels conducted to a decreased cooperation in prisoner's dilemma (Wood, Rilling, Sanfey, Bhagwagar, & Rogers, 2006). It has been hypothesized that serotonin affects our beliefs about others which will influence cooperative behavior (Crockett & Cools, 2015). A previous aggregation of the state of the art reported consistent activations of dorsal and ventral regions of the insula during social decision-making processing. Specifically, whereas the ventral part was associated with perceived unfairness (UG tasks), the dorsal insula is associated with norm compliance (TG tasks) (Bellucci et al., 2018).

1.1.4. Moral decision-making

Closely related to the concepts of fairness and norm compliance is the topic of moral decision-making. Moral decisions are frequently acknowledged as decisions involving moral principles such as harm, justice, and fairness (Killen, Smetana, & Smetana, 2006). As other forms of decision-making, moral decisions are very complex processes (Garrigan, Adlam, &

Langdon, 2018), which involve an interaction between multiple processes at different time-scales and levels of complexity (J. Greene & Haidt, 2002). Moral choices are typically assessed in paradigms involving moral dilemmas, where individuals are presented with scenarios in which they are asked to choose between a more utilitarian and deontological decisions. As an example of such scenarios, consider the following example: It is wartime. You and your fellow villagers are hiding from nearby enemy soldiers in a basement. Your baby starts to cry, and you cover your baby's mouth to block the sound. If you remove your hand, your baby will cry loudly, and the soldiers will hear. They will find you, your baby, and the others, and they will kill all of you. If you do not remove your hand, your baby will smother to death. Do you consider that it is morally acceptable to smother your baby to death in order to save yourself and the other villagers? In practical terms, not smothering the baby will result in the death of many more people (including the baby himself) than deciding to smother him. As such, this should be the wisest choice in a dilemma like this. However, if you are like the most people, you will find this dilemma difficult to solve.

The difficulty in deciding result from conflict between dissociable psychological processes (Cushman & Greene, 2012). The dual-process theory has been established as one of the most widely accepted theories of moral decision-making (J. D. Greene, Sommerville, Nystrom, Darley, & Cohen, 2001). According to this view, when deciding in moral scenarios, individuals make moral decisions according to both, sometimes conflict, automatic (emotional) responses and more controlled (cognitive) responses (J. D. Greene, Morelli, Lowenberg, Nystrom, & Cohen, 2008). Whereas non-utilitarian, or deontological, decisions are driven by automatic processing, utilitarian decisions are driven by cognitive processes (J. D. Greene, 2008). Supporting this view, previous studies in patients characterized by "emotional blunting" demonstrate are more likely to engage in utilitarian decisions than healthy individuals (Mendez, Anderson, & Shapira, 2005). In a similar fashion, patients with focal lesions of the VMPFC were reported to exhibit an abnormally heightened patterns of utilitarian judgements in similar moral dilemmas situations (Koenigs et al., 2007). A similar behavioral profile was observed after emotional induction, where individuals who are presented with emotional stimuli of positive valence have higher odds of choosing utilitarian responses to moral dilemmas (Valdesolo & DeSteno, 2006). Complementing this evidence, previous studies demonstrate that the manipulation of cognitive load, while not altering the proportion of utilitarian judgments, selective increases the reaction time for such decisions (J. D. Greene et al., 2008).

These findings seem to provide support for the idea that more decisions are primarily motivated by emotional drivers, which are later justified by cognitive, utilitarian, reasons (Haidt, 2001). A different perspective suggests that these decisions represent the competitions between appraisal (cognitive and affective) systems, where the winning system takes control of the decisions (J. D. Greene, Nystrom, Engell, Darley, & Cohen, 2004). A more recent hypothesis suggest that moral decisions resemble typical economic decision-making scenarios, where cognitive and emotional processes are computed independently in different brain regions and are then integrated on the VMPFC which will be in charge for the computation of value (Clithero & Rangel, 2013; Hutcherson, Montaser-Kouhsari, Woodward, & Rangel, 2015).

Two recent meta-analysis have aggregated the neurobiological mechanisms underlying moral decision-making. The first reveals that the left middle temporal gyrus (MTG), left precuneus, right MFG, right MTG, right inferior frontal gyrus (IFG) and left caudate display consistent patterns of activation during moral decisions (Garrigan, Adlam, & Langdon, 2016). More recently, Eres and colleagues (2018) identified a meta-analytic map corresponding to a global morality network, in which the authors report consistent activation in the vmPFC, dorsomedial prefrontal cortex (dmPFC), temporo-parietal junction (TPF), precuneus and left amygdala (Eres, Louis, & Molenberghs, 2018).

Even though the study of moral decision-making provides information of upmost relevance for the complexity of decision-making behavior, it is worthwhile mentioning that the experimental paradigms implemented to address such form of decisions differ from other decision-making scenarios in several important ways. Namely, these experimental paradigms are characterized by a large heterogeneity on the type of tasks being used. First, the presentation of the moral decision-making stimuli is typically implemented in the form of long descriptive texts – as the moral dilemma previously presented – which is likely to recruit cognitive processes. Second, the moral decision-making scenarios can be framed in terms of personal vs impersonal situations. Third, the type of responses varies from choosing between alternatives or subjective ratings regarding the adequacy or inadequacy of a described situation. In addition, the subjects can be asked to respond either with respect to his/her own preference or according to the adequacy of the action, independently of his/her preference. For all these reasons and aiming to simplify the message of this manuscript, we decided not to include the aggregation of moral decision-making literature.

1.2. The current study

Despite the advances in the understanding of the neurobiological mechanisms of decision-making, much remains to be explored. The publication of meta-analytic studies on this topic has allowed the accommodation of results from multiple studies on distinct processes of decision-making. However, an integrative perspective of decision-making, considering its complex structure is yet lacking in the literature.

Our study was intended to provide a comprehensive analysis of the neural correlates of decision-making. We focused on the characterization of the mechanisms underlying the modulators of goal-directed behavior, focusing on the role of risk, uncertainty and on social modulators. Following the definition of modulators of the goal-directed system proposed by Rangel and collaborators, we will approach three main components: risk/uncertainty (Study 2.1), time (Study 2.2) and social modulators (Study 2.3).

Finally, conjunction analyses were implemented with the goal of assessing the correspondence between the different meta-analytic maps obtained for each study.

2. Methods

2.1. Data sources

The literature search was performed in multiple online databases, including PubMed, Scopus and ScienceDirect, to identify relevant studies in the context of decision-making. The following keywords were used: “magnetic resonance imaging”, “fMRI”, “neuroimaging” for the different modulators. For risk and uncertainty, this search was complemented with the keywords: “risk” and “uncertainty”; for delay discounting: “delay”, “discounting” and “intertemporal”. For social modulators, we replicated a recently reported strategy (Bellucci et al., 2018), which divides social decision-making in two main domains: trust and reciprocity (with the keywords: “trust”,

"trustor", "investor", "trustee", "trustworthiness" and "reciprocity") and responses to fairness (with the keywords: "normative decision-making", "fair", "altruistic punishment", and "ultimatum game". Additional sources included the Neurosynth and BrainMap (Laird, Lancaster, & Fox, 2005) databases, references from screened studies and from reviews on the topics of interest. Studies obtained from more than one database were identified as duplicates. Potential studies were initially screened based on titles and abstracts. Bibliographic references from these articles were systematically searched.

2.2. Inclusion/Exclusion criteria

A study was included if it (1) was published in English language, in a peer-reviewed journal; (2) used validated tasks to assess goal-directed/habit-based decision-making (Study 1), risk/uncertainty (Study 2.1), delay discounting (Study 2.2), social decision-making (Study 2.3); (3) reported stereotactic coordinates (MNI or Talairach) between contrasting conditions, (Study 1: goal-directed vs habit-based; Study 2.1: risk-aversion vs risk-seeking; Study 2.2: immediate vs delayed outcomes; Study 2.3: fair vs unfair monetary offers); (4) used a sample size of more than five individuals; and (5) used whole-brain analyses, *i.e.,* studies reporting results based on ROI analyses were not included. The process of article selection for each study is presented in a PRISMA diagram (Fig. 2).

2.2. Data extraction

A structured databased was constructed to extract the characteristics from individual studies, including sample characteristics (*i.e.,* participants' age, proportion of male/female participants and level of education), characteristics of the tasks of each study, behavioral results and coordinates of significant findings. Study coordinates were aggregated in Montreal Neurological Institute (MNI) space. In cases where foci were reported in Talairach space, a conversion into MNI was conducted, using mni2tal (Brett, Leff, Rorden, & Ashburner, 2001).

2.3. CBMA algorithms

The Activation Likelihood Estimation (ALE) algorithm (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012) was selected to identify regions of consistent activation, using the GingerALE software (Eickhoff et al., 2009). ALE has been extensively used as a CBMA method (Laird et al., 2005). This approach allows the aggregation of individual experiments, through the interpretation of foci as spatial probability distributions. The contribution of each study is weighted according to each study's sample size – as such, studies with higher sample sizes will have smaller Gaussian distributions and will represent a more reliable approximation of the real activations (Bellucci et al., 2018; Eickhoff et al., 2009).

3. Results

Articles included in each meta-analysis are presented in Tables 1 (risk and uncertainty), 3 (delay discounting) and 5 (social decision-making). Results of individual meta-analyses are summarized below.

Table 1. Included studies in the meta-analytic aggregation of decision-making under risk and uncertainty

Author	Year	N	% Females	# Foci
Banji et al.	2010	14	50.00%	1
Cohen et al.	2005	16	43.75%	5
Elliot et al.	1999	8	25.00%	19
Feinstein et al.	2006	16	50.00%	2
Hosseini et al.	2010	40	7.50%	19
Hsu et al.	2005	16	18.75%	12
Huettel et al.	2005	12	25.00%	10
Jung et al.	2014	24	33.33%	11
Koch et al.	2008	28	60.71%	6
Krug et al.	2014	64	42.19%	13
Paulus et al.	2001	12	16.67%	10
Payzan-LeNestour et al.	2013	18	50.00%	8
Schlosser et al.	2009	12	0.00%	7
Volz et al.	2003	16	31.25%	9
Volz et al.	2004	12	58.33%	14

N – sample size; # Foci – number of foci in each experiment

3.2. Study 2.1: Decision-making under risk and uncertainty

A total of 15 studies (146 foci, 305 subjects) were included in the CBMA of studies in risk and uncertainty (Table 1). The meta-analytic aggregation of studies involving risk and uncertainty revealed consistent patterns of brain activation in several brain regions of the right hemisphere, including: the insula, inferior (BA 47 and BA 40) and middle frontal gyrus (BA 8), as well as the medial dorsal nucleus.

Table 2. Results from the Activation Likelihood Estimation (ALE) for risk and uncertainty

Cluster #	Volume (mm^3)	Extrema Value	x	y	z	Label
1	2344	0.0195	34	24	2	RH.Sub-lobar.Insula.Gray Matter.BA 13
		0.0116	54	18	-4	RH.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter
		0.0098	40	22	-14	RH.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.BA 47
2	1032	0.0176	48	-52	46	RH.Parietal Lobe.Inferior Parietal Lobule.Gray Matter.BA 40
3	880	0.0165	6	28	44	RH.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.BA 8
4	736	0.0162	10	-14	8	RH.Sub-lobar.Thalamus.Gray Matter.Medial Dorsal Nucleus

RH – right hemisphere; BA – Broadmann area

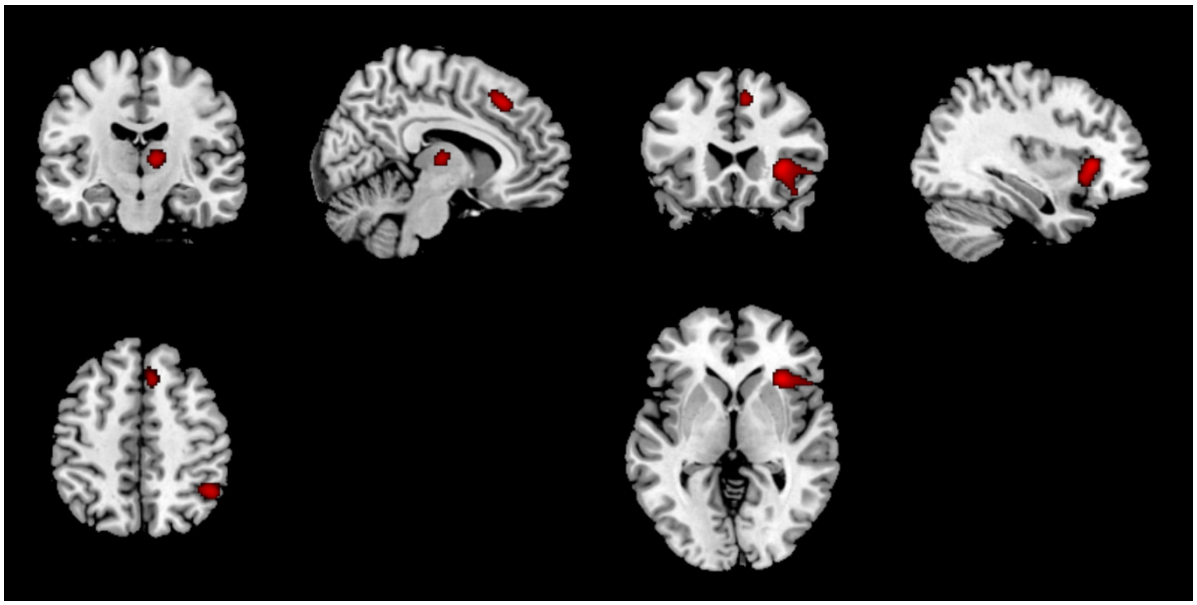

Figure 2. Results from the Activation Likelihood Estimation. Four significant clusters were obtained: the first with peaks on right insula and right inferior frontal gyrus, the second with the peak on the right inferior parietal lobule, the third with the peak on the right medial frontal gyrus, the last with the peak on the medial dorsal nucleus of the right hemisphere.

3.3. Study 2.2: Delay discounting

Seventeen studies, corresponding to 29 experiments (404 foci) were included in the CBMA of DD studies, representing contrasts focusing on decisions for larger delayed rewards against control conditions (*e.g.,* visualization of fixation crosses) or conditions in which the individuals decide for smaller immediate rewards. Four clusters of consistent brain activation were identified: the first was located in a posterior cingulate, comprising the left and right hemispheres; the second cluster had two peaks on the left parietal lobe (BA 40); the other two peaks were located in middle and inferior divisions of the frontal gyrus, encompassing BA 9 and BA 46 (Table 3, Figure 3).

Table 3. Included studies in the meta-analytic aggregation of delay-discounting

Author	Year	N	% Females	# Foci
Christakou et al.	2011	40	0%	11
Onoda et al.	2011	30	53%	12
Sripada et al.	2011	20	0%	15
Peters and Buchel	2010	30	50%	25
				19
Bickel et al.	2009	30	70%	21
				20
				23
Peters and Buchel	2009	22	64%	13
				56
Pine et al.	2009	24	50%	22
				7
				7
				2
				10
Xu et al.	2009	20	50%	19
				18
Hoffman et al.	2008	42	29%	11
Luhmann et al.	2008	20	65%	5
Weber and Huettel	2008	23	48%	5
Boettinger et al.	2007	19	42%	1
Kable and Glimcher	2007	10	60%	22
Monterosso et al.	2007	29	33%	6
				5
Wittman et al.	2007	13	62%	7
McClure et al.	2004	14		10
Tanaka et al.	2004	20	10%	7
				14
				15

N – sample size; # Foci – number of foci in each experiment

A complementary analysis also evidenced consistent patterns of brain activation across regions such as the left caudate, right putamen and thalamus (Figure 3). Nevertheless, it is important to highlight that these findings were observed, considering an un-corrected significance level ($p<.001$ with a minimum volume of 100 mm^3) (Figure 3).

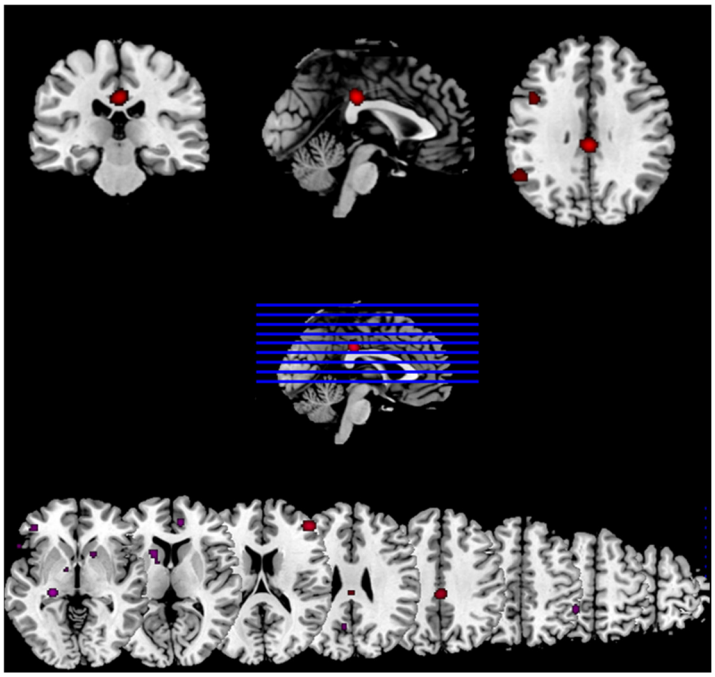

Figure 3. Results from the Activation Likelihood Estimation. Four significant clusters were obtained: the first with peaks on right insula and right inferior frontal gyrus, the second with the peak on the right inferior parietal lobule, the third with the peak on the right medial frontal gyrus, the last with the peak on the medial dorsal nucleus of the right hemisphere. In violet, uncorrected significant results are displayed.

Table 4. Results from the Activation Likelihood Estimation (ALE) for delay discounting

Cluster #	Volume (mm^3)	Extrema Value	x	y	z	Label
1	1192	0.0386	0	-28	34	LH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 31
2	1096	0.0202	-56	-46	38	LH.Parietal Lobe.Supramarginal Gyrus.Gray Matter.BA 40
		0.0189	-56	-54	34	LH.Parietal Lobe.Supramarginal Gyrus.Gray Matter.BA 40
3	896	0.0305	46	42	18	RH.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.BA 46
4	848	0.0209	-42	10	28	LH.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.BA 9
		0.0188	-44	14	34	LH.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.BA 9

LH – left hemisphere; RH – right hemisphere; BA – Broadmann area

Table 5. Included studies in the meta-analytic aggregation of social decision-making

Author	Year	N	% Females	# Foci
Aimone et al.	2014	30	50%	3
		30		2
		30		2
		8		1
Kang et al.	2011	16		4
		16		6
		16		9
Lauharatanahirun et al.	2012	30		9
McCabe et al.	2001	6		1
Stanley et al.	2012	40	0.55	8
		40		2
		40		2
		40		3
Baumgartner et al.	2011	32		17
Civai et al.	2012	19		12
Corradi-Dell'Aqua et al.	2016	19		21
Farmer et al.	2016	18		6
Fatfout et al.	2016	23		18
Feng et al.	2016	40		10
Gospic et al.	2011	17		4
Gradin	2014	25		10
Guo et al.	2013	18		10
Guo et al.	2013	21		13
Gurogu et al.	2011	68		9
Halko et al.	2009	23		22
Harlé and Sanfey	2012	38		12
Haruno et al.	2014	62		4
Hu et al.	2015	23		4
Kirk et al.	2016	50		11
Krik et al.	2011	40		11
Roalf	2010	27		8
Sanfeyet al.	2003	19		17
Servaas et al.	2015	114		32
Verdejo-Garcia et al.	2015	19		4
Verdejo-Garcia et al.	2015	44		13
White et al.	2014	21		7
White et al.	2013	20		8
Wu et al.	2014	18		7
Zheng et al.	2014	25		15
Zhou et al.	2014	28		4

N – sample size; # Foci – number of foci in each experiment

3.4. Study 2.3: Social decision-making

3.4.1. Norm compliance

For the UG, a total of 34 studies (365 foci) were included in the unfair>fair contrast and 15 studies for the fair>unfair contrast (Table 6, Figure 4). This set of studies represents experiments with non-iterative interactions (*i.e.,* each partner in the UG is only involved in only one decision-making scenario). While this strategy captures one-off social interactions, it does not assess the complexity of bidirectional and reciprocal nature of repeated exchanges, which are present in real-life scenarios. Here we aimed to conduct a more simplistic approach. The reasoning behind this relies on the fact that repetitive iterations are likely to motivate long-term strategic decision-making, whereas each decision-making scenario is part of a more complex sequential process.

Table 6. Results from the Activation Likelihood Estimation (ALE) for norm compliance

Cluster #	Volume (mm^3)		x	y	z	Label
1	2992	0.0436	34	24	-4	RH.Sub-lobar.Insula.Gray Matter.*
2	2392	0.0381	-4	16	46	LH.Frontal Lobe.Medial Frontal Gyrus.Gray Matter.BA 32
		0.0326	6	20	42	RH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 32
3	1552	0.034	-30	22	0	LH.Sub-lobar.Claustrum.Gray Matter.*
4	312	0.0287	8	28	24	RH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 32
5	216	0.0277	36	50	16	RH.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.BA 10
6	160	0.0256	-8	58	20	LH.Frontal Lobe.Superior Frontal Gyrus.Gray Matter.BA 9
7	152	0.0232	40	34	26	RH.Frontal Lobe.Middle Frontal Gyrus.Gray Matter.BA 9
8	16	0.0197	-8	24	28	LH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 32

LH – left hemisphere; RH – right hemisphere; BA – Brodmann area

3.4.2. Trust

Regarding TG, a total of 13 articles were included in the meta-analysis for one-shot decisions (*i.e.,* participants made one single proposal to each partner) and 28 studies were considered for iterative decisions (*i.e.,* participants made multiple proposals for the same partner). Sixteen studies were included for decisions to reciprocate. Right insula, precentral,

inferior frontal and cingulate gyri displayed consistent patterns of increased brain activity during TG tasks (Table 7, Figure 5).

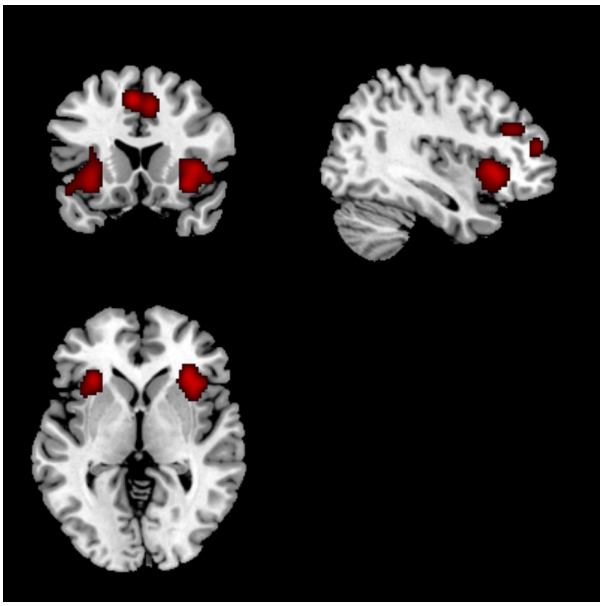

Figure 4. Results from the Activation Likelihood Estimation. Eight significant clusters were obtained.

Table 7. Results from the Activation Likelihood Estimation (ALE) for trust

Cluster #	Volume (mm^3)	Extrema Value	x	y	z	Label
1	1480	0.0188	42	18	2	RH.Sub-lobar.Insula.Gray Matter.BA 13
		0.0105	50	14	4	RH.Frontal Lobe.Precentral Gyrus.Gray Matter.BA 44
		0.0095	42	32	2	RH.Frontal Lobe.Inferior Frontal Gyrus.Gray Matter.BA 13
2	856	0.0142	6	12	40	RH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 32
		0.0108	-4	18	40	LH.Limbic Lobe.Cingulate Gyrus.Gray Matter.BA 32

LH – left hemisphere; RH – right hemisphere; BA – Broadmann area

4. Discussion

In this work, we performed a comprehensive systematic review and a coordinate-based meta-analytic aggregation of neuroimaging studies addressing different modulators of goal-directed decision-making. We aggregated studies assessing the impact of risk/uncertainty, time discounting and social modulators (trust/reciprocity and norm compliance) on brain patterns of

activation. We observed that there were consistent patterns of brain activation of the right insula in decision-making scenarios involving risk and uncertainty, but also in paradigms of social decision-making.

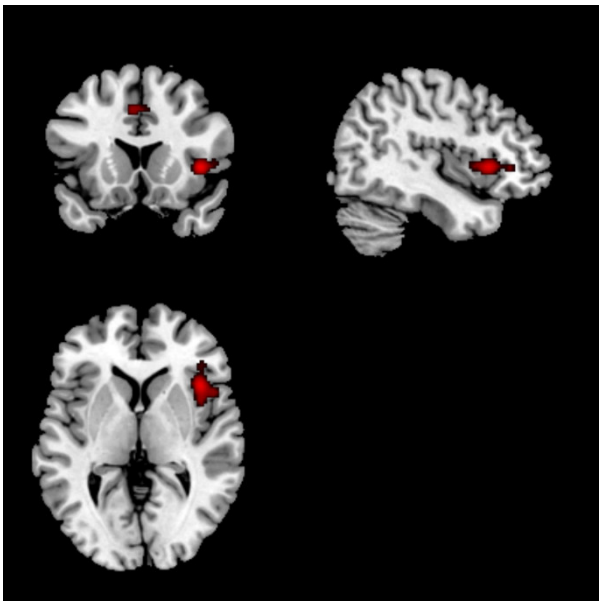

Figure 5. Results from the Activation Likelihood Estimation. Eight significant clusters were obtained.

One important consideration related with temporal discounting studies pertains to the relevance of tasks' framing. Even though we did not have enough experiments to statistically compare this, it has been reported that the comparison between delayed and immediate outcomes is dependent on where the proposal is framed as a reward or as a loss (Xu, Liang, Wang, Li, & Jiang, 2009). Following a previously reported strategy, to maximize the statistical power of our analysis, we decided not to focus on the distinction between gains and losses (Wesley & Bickel, 2014). It has been previously reported that specific modulators of the goal-directed system of decision-making – namely DD – are intrinsically connected to cognitive aspects (Bickel, Yi, Landes, Hill, & Baxter, 2011), such as working memory and that there is an overlap between the activation maps underlying these domains (Wesley & Bickel, 2014). The meta-analytic maps resulting from this comprehensive aggregation of neuroimaging studies also point to a relevant role of emotion-related processing on different modulators of decision-making. Cumulative evidence has supported the notion that emotion plays a crucial role on decision-making behavior. However, the scientific literature tackling this interference, by assessing the

role of experimental emotion induction on decision-making patterns across different value modulators, is still quite underexplored, both behaviorally and neurobiologically.

Regarding social decision-making tasks, we focused on the study of tasks related with trust/reciprocity and norm compliance, while not tackling the neurobiological mechanisms associated with other aspects of social decision-making, such as donation. Nevertheless, previous research has highlighted that there are dissociable neurobiological processes underlying altruistic punishment and donation – as such, the systematic aggregation of these differential processes constitute a question for future research (Moll et al., 2018). Still within the social modulators of decision-making, we summarized the consistent patterns of brain activation associated with unfair against fair offers – however, it would be important to further distinguish between the consistent patterns associated with accepted against rejected unfair offers.

Furthermore, even though it is acknowledged that the study of decision-making constitutes an important means to identify potential targets for the treatment of neuropsychiatric disorders, no meta-analytic work has aggregated the results of individual studies with neuropsychiatric patients. Whereas we initially considered the possibility of conducting this work, a preliminary literature search evidenced that the amount of studies focusing on individual pathologies would under-power a quantitative aggregation of neuroimaging findings.

Meta-analytic investigations are acknowledged as having a high level of evidence by allowing to consider the between-studies' variability. Nevertheless, it is of upmost relevance to recognize that the reproducibility of meta-analytic investigations is a considerable challenge across different fields of science (Lakens, Hilgard, & Staaks, 2016). As the complexity of information being obtained from each study increases, more challenges will be imposed to the aggregation of multiple studies. This may constitute a specific issue on the aggregation of coordinate-based neuroimaging investigations, where different experiments report the results in light with different coordinate systems (*i.e.,* MNI and Talairach), considering different (uncorrected or corrected) thresholds for statistical significance, where the experimental tasks have their own specificities and so on and so forth. While we cannot account for some of these issues, we consider that reporting the coordinates from each of the individual studies, the coordinate system and the method for defining statistical significance – as we reported in this meta-analytic investigation – may allow future investigations to properly reproduce meta-analyses of coordinate-based meta-analysis or to work on top of these works. Allowing meta-analytic data

to be openly available enables other researchers to check whether the data from individual studies was properly extracted, and whether study characteristics were accurately coded (Lakens et al., 2016). As such, this strategy may bring important benefits for this field, by promoting cumulative evidence throughout an improvement of disclosure of data (Campbell, Loving, & Lebel, 2014).

This work was focused on the identifications of consistent foci associated with task-related patterns of brain activity. Current conceptualizations have been highlighting the importance of addressing brain functioning as a network. As such, while the variability of different methods for assessing task-related functional connectivity – covering several methodological approaches – imposes additional challenges for the quantitative aggregation of these findings, those approaches may provide further advances in understanding a more in-depth characterization of the human behavior (Gonzalez-Castillo & Bandettini, 2018). Regarding this same topic, recent reports have been promoting the relevance of dynamic approaches for the examination of resting-state and task-related functional connectivity – revealing that the human brain signals transition between states of connectivity over time (Zalesky, Fornito, Cocchi, Gollo, & Breakspear, 2014). While the origin of such oscillations are still not completely understood, it has been demonstrated that the performance during cognitive tasks is associated with a dynamic organization of the brain architecture (Shine et al., 2016). To the best of our knowledge, such approach has not yet extended to the study of decision-making processing, which constitutes an important opportunity for future research.

Another outstanding issue pertains to the aggregation of studies assessing the relationship between intrinsic brain patterns, such as brain structure or patterns of resting-state functional connectivity. This approach has been previously proposed as a relevant strategy for the identification of the brain nodes associated with different psychological domains, as it is independent of factors such as attention or effort-related processes. The number of studies implementing this strategy in the context of the modulators of decision-making is still yet under-explored, which precluded a quantitative aggregation of such studies. The aggregation of intrinsic brain patterns associated with task-independent functional connectivity has been previously included in the same pool of task-related fMRI studies (Wesley & Bickel, 2014). Nevertheless, according to the abovementioned reasons related with attention-dependent processing that can interfere with one modality, but not the other, we decided not to replicate this strategy.

Even though we intended to provide a comprehensive characterization of decision-making processing, there were some topics that were not tackled in this review of the literature. Here, we focused on the neurobiological correlates of different value modulators of decision-making at the time of action selection, *i.e.*, when subjects decide between different alternatives. It would be also relevant to aggregate the findings from the feedback phase, *i.e.,* when subjects realize the outcomes. A more conceptual note pertains to the fact that whereas we focused on social modulators of goal-directed decision-making, we did not include studies focused on moral decision-making. This decision was based on the fact that there is a large variability on the type of task that is usually implemented.

Finally, given the relevance of decision-making in our everyday living, it is of crucial importance to characterize pathological forms of decision-making. An increasing amount of evidence has highlighted the relevance of impaired decision-making behavior as one key feature of several psychological conditions. This is particularly pronounced in conditions characterized by high impulsivity – such as ADHD, substance addiction or antisocial personality disorder – or those marked by compulsive behaviors – such as obsessive-compulsive disorder (OCD), which is proposed to be a disorder of decision-making (Cavedini, Gorini, & Bellodi, 2006; Sachdev & Malhi, 2005). As such, a proper characterization of the neurobiological mechanisms underlying impaired decision-making processing in these conditions constitutes an important challenge for future research.

In sum, this work allowed us to aggregate the meta-analytic brain maps of distinct value modulators of goal-directed decision-making. We conclude that there is a substantial overlap between these maps and that they present patterns of meta-analytic connectivity modelling consistent with brain networks with relevance for emotional processing, highlighting the relevance of emotional-related processes for decision-making behavior.

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Chapter 2. OCD as a proxy to impaired decision-making behavior

CHAPTER 2.1

The neural correlates of obsessive-compulsive disorder: a multimodal perspective

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ORIGINAL ARTICLE

The neural correlates of obsessive-compulsive disorder: a multimodal perspective

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Obsessive-compulsive disorder (OCD) is one of the most debilitating psychiatric conditions. An extensive body of the literature has described some of the neurobiological mechanisms underlying the core manifestations of the disorder. Nevertheless, most reports have focused on individual modalities of structural/functional brain alterations, mainly through targeted approaches, thus possibly precluding the power of unbiased exploratory approaches. Eighty subjects (40 OCD and 40 healthy controls) participated in a multimodal magnetic resonance imaging (MRI) investigation, integrating structural and functional data. Voxel-based morphometry analysis was conducted to compare between-group volumetric differences. The whole-brain functional connectome, derived from resting-state functional connectivity (FC), was analyzed with the network-based statistic methodology. Results from structural and functional analysis were integrated in mediation models. OCD patients revealed volumetric reductions in the right superior temporal sulcus. Patients had significantly decreased FC in two distinct subnetworks: the first, involving the orbitofrontal cortex, temporal poles and the subgenual anterior cingulate cortex; the second, comprising the lingual and postcentral gyri. On the opposite, a network formed by connections between thalamic and occipital regions had significantly increased FC in patients. Integrative models revealed direct and indirect associations between volumetric alterations and FC networks. This study suggests that OCD patients display alterations in brain structure and FC, involving complex networks of brain regions. Furthermore, we provided evidence for direct and indirect associations between structural and functional alterations representing complex patterns of interactions between separate brain regions, which may be of upmost relevance for explaining the pathophysiology of the disorder.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is one of the most disabling psychiatric conditions, impacting occupational, academic and social functioning[1] and affecting 2 to 3% of the worldwide population.[2] OCD is characterized by the occurrence of obsessions (intrusive, persistent and inappropriate thoughts, urges or images) and compulsions (repetitive or ritualistic behaviors or mental acts performed to reduce the anxiety caused by the obsessions).[3,4] Despite the availability of pharmacological and cognitive-behavioral interventions, these treatments are not effective for a significant number of patients.[5] This highlights the limited understanding of the neurobiological mechanisms of OCD.[6]

The pathophysiology of OCD has been widely conceptualized within the cortico-striato-thalamo-cortical (CSTC) model.[7] According to this model, tracts from frontal regions project to the striatum and then, travel through direct and indirect pathways to the thalamus and project back to the frontal regions. This model has been corroborated by several reports of structural and functional alterations observed in magnetic resonance imaging (MRI) studies. In particular, volumetric alterations within the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) and thalamus have been reported in patients (for example, refs. 8–10). Furthermore, early evidence from functional imaging studies indicated an increased metabolism and hyperactivity in several brain regions in OCD patients during task performance, including the basal ganglia (BG),[11,12] OFC[13] and ACC.[14] On the opposite, a decreased activation in the dorsolateral prefrontal cortex (DLPFC)[15] and parietal cortex[16–19] has been described. Emerging evidence suggests a broader cortical dysfunction, involving structural and functional alterations of the anterior insula, lateral and medial temporal lobe regions.[20] Furthermore, recent multimodal meta-analytic evidence highlights the relevance of the cerebellum and the parietal cortex for the OCD pathophysiology.[21]

Resting-state fMRI (rs-fMRI) studies have also provided important biomarkers of OCD. For instance, alterations in the normal patterns of functional connectivity (FC) in resting-state networks (RSNs) have been reported in children with OCD, including a significantly increased connectivity between the dorsal striatum and ventromedial frontal cortex, and a decreased FC between dorsal striatum and medial dorsal thalamus to rostral and dorsal ACC, respectively.[22] In addition, increased FC within the auditory and cingulate networks was also reported in a pediatric sample.[23] Adult OCD individuals exhibited decreased FC of the dorsal striatum and lateral PFC, and of the ventral striatum with ventral tegmental area,[24] as well as a decreased dorsal ACC-right anterior operculum FC during rest.[25] Altered FC in the default-mode network (DMN) has been reported, particularly its connections with OFC and ACC,[25,26] and with middle frontal gyrus and

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putamen.[26] Moreover, FC alterations between frontoparietal/ventral attention network (VAN) and the structures comprising the DMN, thalamus, lateral frontal cortex and somatosensory/motor regions were observed.[20] Using a graph-theory approach, drug-free patients were found to present a diminished FC between the DMN and frontoparietal regions;[27] interestingly, these alterations were abolished after SSRI treatment.

Altogether, the abovementioned results suggest that a large variety of brain areas and circuits are involved in the pathophysiology of the disease. In particular, FC abnormalities have been mainly observed in orbitofrontal, cingulate, striatal and default-mode regions. Nevertheless, these results were observed using theoretically driven investigations. To the best of our knowledge, the use of whole-brain exploratory approaches to assess FC patterns in OCD patients is scarce, with few notable exceptions.[28,29]In these studies, OCD patients were characterized by a reduced FC within the lateral prefrontal cortex and an increased FC within the dorsal striatum and thalamus, as well as with a hyperconnectivity between basal ganglia and cerebellar regions. Nevertheless, none of the abovementioned strategies integrated structural findings in their analyses. Thus, despite the variety of studies investigating structural and functional MRI patterns in OCD patients, a comprehensive integration of distinct modalities is still unclear. The use of this multimodal/integrative approach may be of upmost relevance, as it may provide useful information on how distinct MRI modalities (that is, brain structure and function) are associated with each other.[30] Consequently, it will enable a further exploration of our understanding of the pathophysiological core features of OCD. With this purpose, we conducted a multimodal study, using voxel-based morphometry and whole-brain functional connectivity analyses, respectively, in which structural and FC data were integrated in mediation models. We hypothesize that OCD patients will be characterized by disrupted structural and FC patterns of large-scale brain networks, as manifested by alterations at the whole-brain level. Furthermore, in accordance with recent developments on the study of OCD, it is anticipated that FC alterations will be observed in networks comprising regions outside of the CSTC model.

MATERIALS AND METHODS

Participants

A sample of 80 subjects (40 OCD patients, 40 controls) participated in this study. Healthy controls were recruited to match OCD patients for age, sex, educational level and ethnical origin. All the participants were right-handed and had no history of neurological or comorbid disorders. OCD patients were characterized with a comprehensive clinical assessment. The diagnosis of the disorder was established by experienced psychiatrists, using a semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-TR. Then, the Mini-International Neuropsychiatric Interview (MINI), a short structured diagnostic interview, was administered to confirm OCD diagnosis and to identify any current psychiatric (non-OCD) comorbidity. Patients that met criteria for additional Axis I psychiatric disorders at the time of the study were not included in this study. The severity of the disease was assessed using the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS[31]). Hamilton Anxiety Rating Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D) were used to assess anxiety and depression symptoms, respectively. All OCD patients were under medication: the majority of patients (72.2%) was receiving SSRI medication (fluxomanine, 150–300 mg day^{-1}; fluoxetine, 40–80 mg day^{-1}; sertraline: 100–200 mg day^{-1}), 11.1% of the sample was receiving TCA (clomipramine, 150–300 mg day^{-1}), 16.7% was receiving combined pharmacological intervention. All the patients were receiving stable doses for at least three months prior to the imaging session. The sample characterization is presented on Table 1.

The study was conducted according to the Declaration of Helsinki principles and was approved by the Ethics Committee of Hospital de Braga (Portugal). The study goals were explained, and written informed consent was obtained from each participant.

Table 1. Socio-demographic and clinical characteristics of patients with OCD and HC

Characteristic	*OCD (n = 40)*	*HC (n = 40)*	*Difference*
Age, years	26.28 ± 6.62	26.45 ± 5.39	$t_{(78)} = 0.13$, $P = 0.897$
Education, years	13.53 ± 2.25	14.63 ± 3.20	$t_{(78)} = 1.78$, $P = 0.079$
Sex, *n* (%) males	13 (32.5%)	13 (32.5%)	—
Y-BOCS, total score	24.93 ± 5.69	—	—
Y-BOCS, obsessions	13.48 ± 3.10	—	—
Y-BOCS, compulsions	11.45 ± 3.36	—	—
Age of onset, years	19.41 ± 6.27	—	—
HAM-A, total score	5.10 ± 4.40	—	—
HAM-D, total score	6.05 ± 4.70	—	—
Medication			
% SSRI	72.20%	—	—
% TCA	11.10%	—	—
% combined	16.70%	—	—
Time with medication, months	23.19 ± 28.75	—	—
Motion spikes	7.35 ± 3.95	6.35 ± 3.32	$t_{(78)} = -1.23$, $P = 0.224$

Abbreviation: HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; HC, healthy controls; OCD, obsessive-compulsive disorder; Y-BOCS, Yale–Brown Obsessive Compulsive. Values are presented as mean ± s.d. Spikes are volumes with high motion, discarded while estimating connectivity patterns.

MRI protocol

The imaging sessions were performed at Hospital de Braga using a clinically approved 1.5 T Siemens Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 12 channel receive-only head coil. Details on the imaging parameters are described in the Supplementary Information.

Volumetric analysis

Before any data processing and analysis, all the acquisitions were visually inspected to confirm that they were not affected by significant artifacts and that participants had no gross anatomical abnormalities. For the volumetric analysis, a Voxel-Based Morphometry (VBM) analysis was performed with FSL-VBM (ref. 32, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM), an optimized VBM protocol[33] implemented using tools from the FMRIB Software Library (FSL v5.0.9, www.fmrib.ox.ac.uk/fsl), using the recommended analytical pipeline (Supplementary Information).

Data preprocessing of functional data

Data preprocessing was performed using FSL tools. Images were corrected for slice timing using the first slice as reference and then motion corrected by aligning every volume with the mean volume using a rigid-body (six degrees of freedom) spatial transformation. As a means to further reduce the possible contamination of motion on functional connectivity, motion scrubbing was performed, to identify and exclude time points in which head motion could have a critical impact. Following the recommendations from Van Dijk *et al.*,[34] only participants with < 20 outlier time points were included in the analysis, ensuring that more than 5 min of motion-free data was obtained for each subject. None of the participants exceeded head motion higher than 2 mm in translation or 1° in rotation. Images were non-linearly normalized to the MNI standard space using an indirect procedure (Supplementary Information). Linear regression of motion parameters, mean white-matter (WM) and cerebrospinal fluid (CSF) signal and motion outliers was performed to reduce motion related variance in fMRI signals and the residuals of the regression were used for the subsequent analysis.[35,36] Finally, images were spatially smoothed with a Gaussian kernel of 8 mm full-width at half-maximum (FWHM) and band-pass filtered (0.01–0.08 Hz).

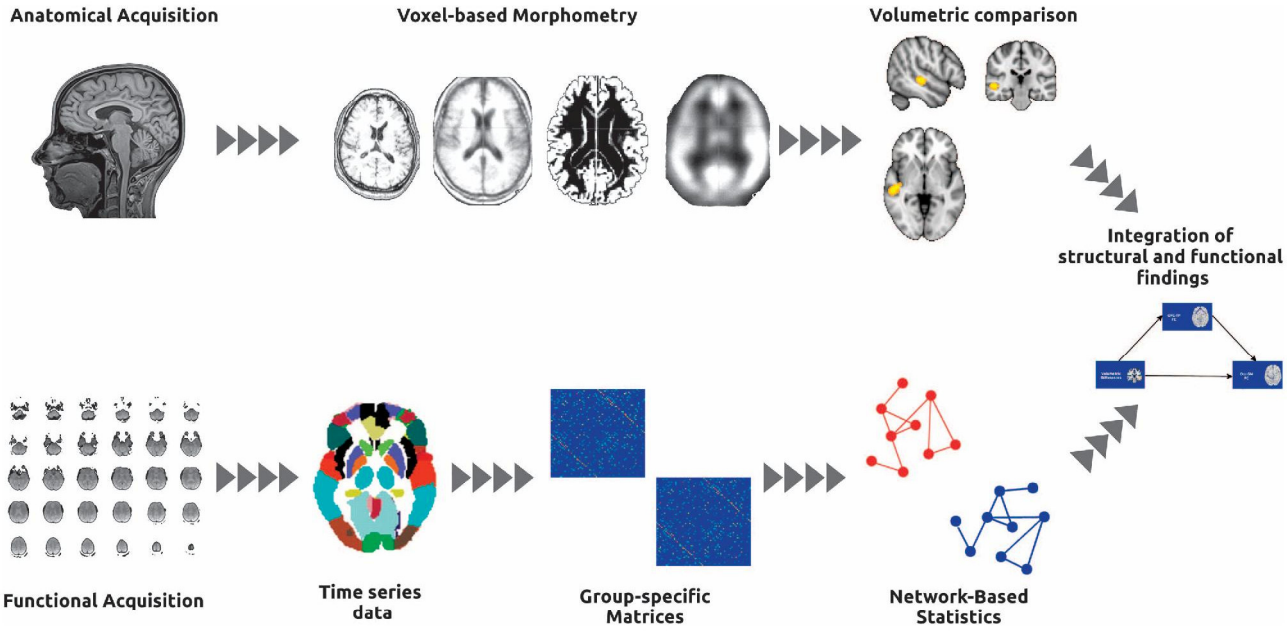

Figure 1. Overview of the methodological approach. Structural and functional magnetic resonance imaging (MRI) sequences were acquired. For the structural acquisitions, a voxel-based morphometry analysis was conducted to detect clusters with significantly between-group differences. For the functional acquisitions, the time-series of Anatomical Automatic Labelling (AAL) cortical and subcortical brain regions was extracted to create group-specific matrices, corresponding to the correlation between regions. Afterwards, a network-based statistic approach was implemented to detect networks with significantly different functional connectivity between groups. As the final step, the structural and functional results were analyzed in integrative models, using mediation analyses.

Whole-brain connectome

Whole-brain functional connectomes were built by extracting the mean time-series of 116 cortical, subcortical and cerebellar regions from the Anatomical Automatic Labelling (AAL) atlas.[37] A symmetric adjacency matrix R was then produced, where each cell r_{ij} corresponded to the correlation coefficient (r) between the time-series of regions i and j. This matrix was then transformed with Fisher's r-to-Z transformation to convert Pearson coefficients r to normally distributed Z-values. Individual matrices were then aggregated for further statistical analysis.

Statistical analysis

Statistical group comparisons on volumetric and functional MRI data were conducted using two-samples t-tests, adjusted for confounding effects. For the different analysis, sex and age were used as between-subjects' covariates.

VBM analysis was performed voxel-wise with a General Linear Model (GLM) using a non-parametric permutation procedure as implemented in the randomise tool from FSL.[38] Threshold-free cluster enhancement (TFCE) was used to detect widespread significant differences, whereas controlling the family-wise error rate (FWE-R) at $\alpha = 0.05$. Each contrast underwent 5.000 permutations.

The identification of significantly different FC subnetworks between groups at the whole-brain connectome was performed through the network-based statistic (NBS) procedure, implemented with NBS.[39] The differences between the adjacency matrices of each group were estimated with 5.000 random permutations, based on two different thresholds for significance: $\alpha = 0.001$ and $\alpha = 0.0001$. Networks were considered significant at $\alpha = 0.05$ family-wise error (FWE) corrected. BrainNet Viewer (http://www.nitrc.org/projects/bnv) was used to display significant networks.[40]

Associations between symptoms' severity and structural/functional findings were evaluated computing Pearson correlations between total Y-BOCS score and findings significantly different between groups.

With the goal of integrating structural and functional findings, mediation models were established. For these models, direct (that is, the impact of the independent on the dependent variable) and indirect effects (that is, the impact of one proposed mediator variable on the key relationship) were evaluated. For both approaches, bootstrap sampling was implemented to generate bias-corrected 95% confidence intervals to estimate indirect and interactive effects.

An overview of the methodological pipeline is summarized on Figure 1.

RESULTS

Sample characteristics

As shown in Table 1, the groups are similar with respect to sex, age and education level. As represented, all the participants were taking medication. The Y-BOCS total score ranged from 11 to 35 ($M = 24.93$, s.d. = 5.69). The groups did not differ on the number of motion outliers ($t_{(78)} = -1.23$, $P = 0.224$).

Volumetric analysis

Results from the VBM analysis revealed that OCD patients had significantly reduced volumes in one cluster comprising 394 voxels with peak on the right temporal middle gyrus, extending to the superior temporal gyrus (Figure 2). We will refer to this region as the superior temporal sulcus (STS). No results of volumetric increases in OCD patients were found.

Whole-brain functional connectivity

Using the most restrict threshold ($P < 0.0001$), it was noted that OCD patients displayed significantly reduced FC in two subnetworks with short-range configurations: the first subnetwork (orbitofrontal-temporal pole subnetwork, OFC-TM) comprised anterior regions, including the bilateral medial orbitofrontal cortex (mOFC), bilateral temporal poles and the subgenual anterior cingulate cortex (sgACC) (Figure 3a; $P = 0.010$); the second subnetwork (occipital-sensorimotor, Occ-SM) was formed by the connection between left postcentral and bilateral lingual gyri (Figure 3a; $P = 0.045$). Using the less restrict threshold ($P < 0.001$), it was observed that these subnetworks were aggregated in a main single network with wide-range properties, which was also constituted by edges connecting occipital and sensorimotor brain regions and also involving edges connecting the temporal middle gyrus to the mOFC (Figure 3b; $P = 0.039$). In contrast, even though no networks with significantly different FC patterns were identified with the more restrict threshold, using the less restrict threshold, a network (thalamic-occipital, Thal-Occ) with marginally

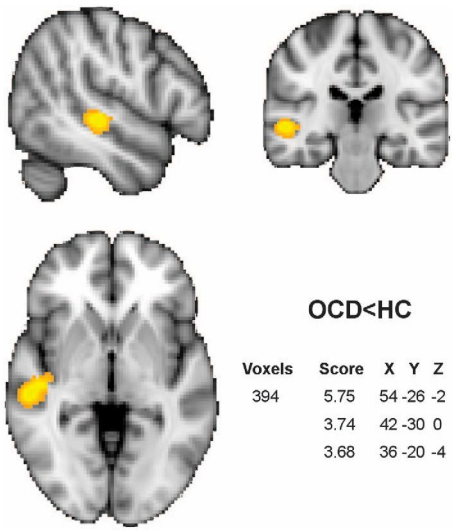

Figure 2. Volumetric differences obtained using a voxel-based morphometry (VBM) analysis. Obsessive compulsive disorder (OCD) patients display significantly reduced volumes in one cluster (with 394 voxels), with peak on the middle temporal gyrus (MTG, $t_{(78)} = 5.75$).

significant increased FC ($P = 0.057$) in OCD patients was identified, encompassing edges connecting the thalamus to occipital inferior, lingual and fusiform gyri (Figure 3d).

Associations between symptom's severity and structural/functional findings

The Y-BOCS total score revealed a significant negative association with the fronto-temporal subnetwork with decreased FC in OCD patients ($r = -0.325$, $P = 0.040$). No associations between symptoms' severity and the other functional and volumetric findings were found.

Mediation effects between structural and functional findings

Bivariate correlations revealed that the volumetric and FC findings were significantly associated (Supplementary Table 1), enabling the test for mediation effects. Different models were conducted, using the volumetric differences as either independent or dependent variables. It was observed that, controlling for confounding effects (sex and age), the mean FC of the OFC-TP subnetwork significantly mediated the association between volumetric differences and the mean FC of the Occ-SM subnetwork (Figure 4a), as observed by a significant indirect between these variables. On the other hand, we could also observe that there was a significant indirect effect of the mean FC of the Thal-Occ subnetwork on volumetric differences within the STS, which was mediated by two mediator variables, corresponding to the mean FC of the Occ-SM and OFC-TP subnetworks (Figure 4b).

DISCUSSION

In this work, we conducted an exploratory multimodal MRI investigation to study volumetric and FC patterns in OCD patients. We observed that OCD patients display volumetric reductions of one cluster comprising the right medial and superior temporal gyri and significantly altered FC in distinct subnetworks, particularly a reduced FC in networks connecting the medial OFC, temporal poles, lingual and postcentral gyri; and on the opposite, patients had increased FC in a network composed of connections involving the thalamus and occipital regions. Mediation analyses revealed that the association between structural findings and specific FC networks were mediated by other FC networks.

Volumetric alterations in OCD patients

We observed that OCD patients display volumetric reductions of one cluster with peak on the right STS, extending to both the medial and superior temporal gyri. This result is corroborated by previous reports, which implicated the superior temporal cortex on the pathophysiology of the disease.[41] Furthermore, in a meta-analytic investigation, it was demonstrated that OCD patients display a reduction of the middle temporal gyrus during the aging process.[42]

Decreased functional connectivity in OCD patients

In our study, a FC network comprising connections between bilateral mOFC and bilateral temporal pole, as well as between the left temporal pole and the sgACC, revealed decreased FC in OCD patients. The mOFC is functionally connected with default-mode network, autonomic and subcortical regions, including the ventral striatum, amygdala and the hippocampus,[43,44] being relevant for multiple psychological processes, including episodic memory, reward, decision-making and fear.[43,45] Previous studies demonstrated bilateral volume reductions[46] and hypo-functioning of the mOFC during extinction recall in OCD.[7] Furthermore, the temporal pole, is directly linked to prefrontal brain regions, through a large white-matter tract, the uncinate fasciculus. Owing to its dense connections with the amygdala and the OFC, the temporal pole is considered an important hub of the affective brain circuit.[47] The temporal pole, together with the sgACC, were implicated in the mental effort to overcome fear.[48] With respect to OCD pathophysiology, these nodes have been previously associated with the severity of harm/checking symptoms[49] and dysfunctional beliefs.[50] A recent report also revealed a decrease in the structural connectivity among these regions in OCD, highlighting the role of emotional processing on the clinical manifestations of the disorder.[51] Altogether, and due to the fact that this subnetwork was significantly associated with the severity of OCD symptoms, it seems reasonable to hypothesize that the reduced link between OFC and these 'affective' hubs may contribute to a deficient emotional processing and a consequent impaired regulation of the anxiety following obsessive thoughts.

Another subnetwork with decreased FC in OCD patients was composed of edges involving bilateral lingual gyrus and the left postcentral. Previous studies reported alterations in functional[52] and structural[53] connectivity patterns of this region in OCD patients. The lingual gyrus was proposed to be involved in the processing of emotionally charged visual stimuli[54] and with the generation of somatic arousal,[55] which is typically dysregulated in disorders of the obsessive-compulsive spectrum.[53] It has been recently hypothesized that its activity is tightly linked to the phenomenology of OCD, where, for instance, intrusive thoughts or images of dirt, provoke strong emotional responses in patients with contamination obsessions.[56] In addition, the activity of the lingual gyrus, together with the amygdala and orbital regions, was reported to be elicited by emotional, unpleasant, stimuli,[57] being also activated during the visualization of fearful faces.[58] Providing further evidence for this hypothesis, it has been demonstrated that the activity of this brain region is altered in psychiatric conditions characterized by anxious[59] and depressive symptoms.[60] Altogether, it is reasonable to hypothesize that this network of reduced FC may underlie an altered emotional processing, particularly related with fear content. Following this hypothesis, the decreased FC between visual and sensorimotor networks herein observed may be contextualized in line with a previous hypothesis suggesting that an exaggerated FC between distinct sensory regions may contribute to a heightened encoding of fear-related stimuli during task performance.[61] Despite the fact

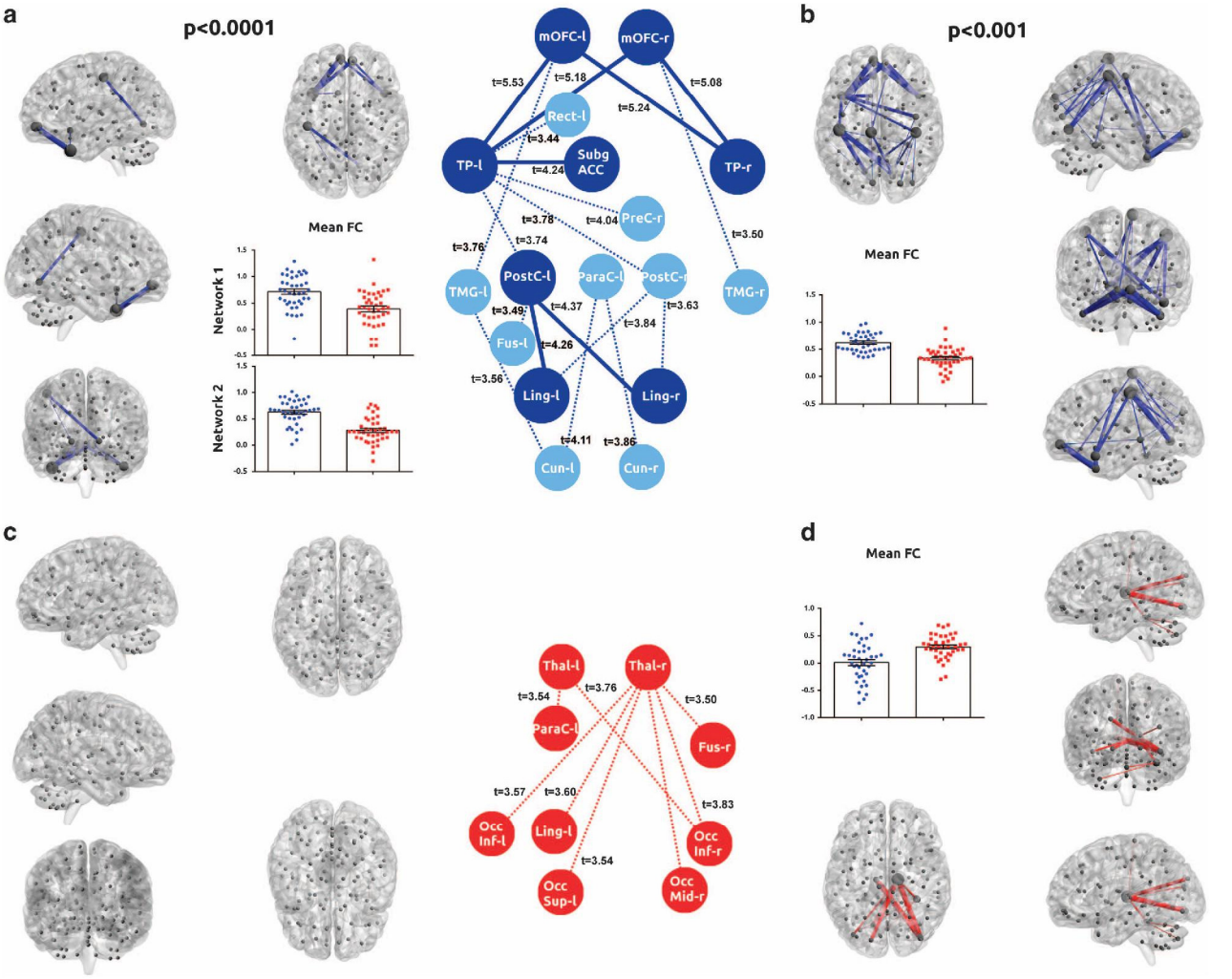

Figure 3. Whole-brain networks with altered functional connectivity (FC) in obsessive-compulsive disorder (OCD) patients, using two primary thresholds: networks with significantly decreased FC (blue) in OCD patients at $P < 0.0001$ (**a**) and $P < 0.001$ (**b**) levels are presented on the top; (**c**) no networks with significantly increased FC was found at the $P < 0.0001$ level; (**d**) a network with significantly increased FC (red) was found in OCD patients at $P < 0.001$ level. Bar graphs correspond to individual levels of mean FC in each group. On the middle, the t-statistic corresponding to each individual edge is represented for networks with increased and decreased FC levels.

that our findings are in apparent contradiction with the above-mentioned report, it is important to note that whereas Wiemer's findings were obtained while subjects were viewing emotional, fear-related stimuli, our results were obtained with the absence of stimuli, that is, during rest. As such, it is reasonable to hypothesize that the abnormal FC between these regions may be context-dependent, being highly connected during the processing of emotional information, and hypoconnected in default brain processing.

Increased functional connectivity in OCD patients: extension of the typical CTSC model

A network with marginally significant increases of FC between thalamic and occipital brain regions was observed in OCD patients. The most widely accepted neurobiological models of OCD rely on an increased cerebral metabolism in circuits involving the thalamus, OFC and the striatum—the CTSC model—which is thought to underlie behavioral alterations in multiple domains, including reward processing, action selection or habit-based functioning. This hypothesis is partially corroborated by our results in which edges with (marginally) significant increases in resting-state FC, connecting the thalamus to cortical regions were found in OCD patients. Furthermore, the involvement of other regions not included in the CTSC model also corroborates more recent models, in which parietal, occipital and cerebellar regions have been identified as relevant for the pathophysiology of the disease.[21]

Integration of structural and functional findings

We observed that the structural and functional findings herein obtained were significantly associated. Nevertheless, it was noted that the associations between structural and specific functional results were significantly mediated by specific FC patterns that altered the relationship between structure and function: the mean FC of OFC-TP subnetwork significantly mediated the association between volumetric differences within the STS and Occ-SM subnetwork (model 1); the mean FC of Occ-SM and OFC-TP subnetworks significantly mediated the association between the mean FC of the Thal-Occ subnetwork and volumetric differences

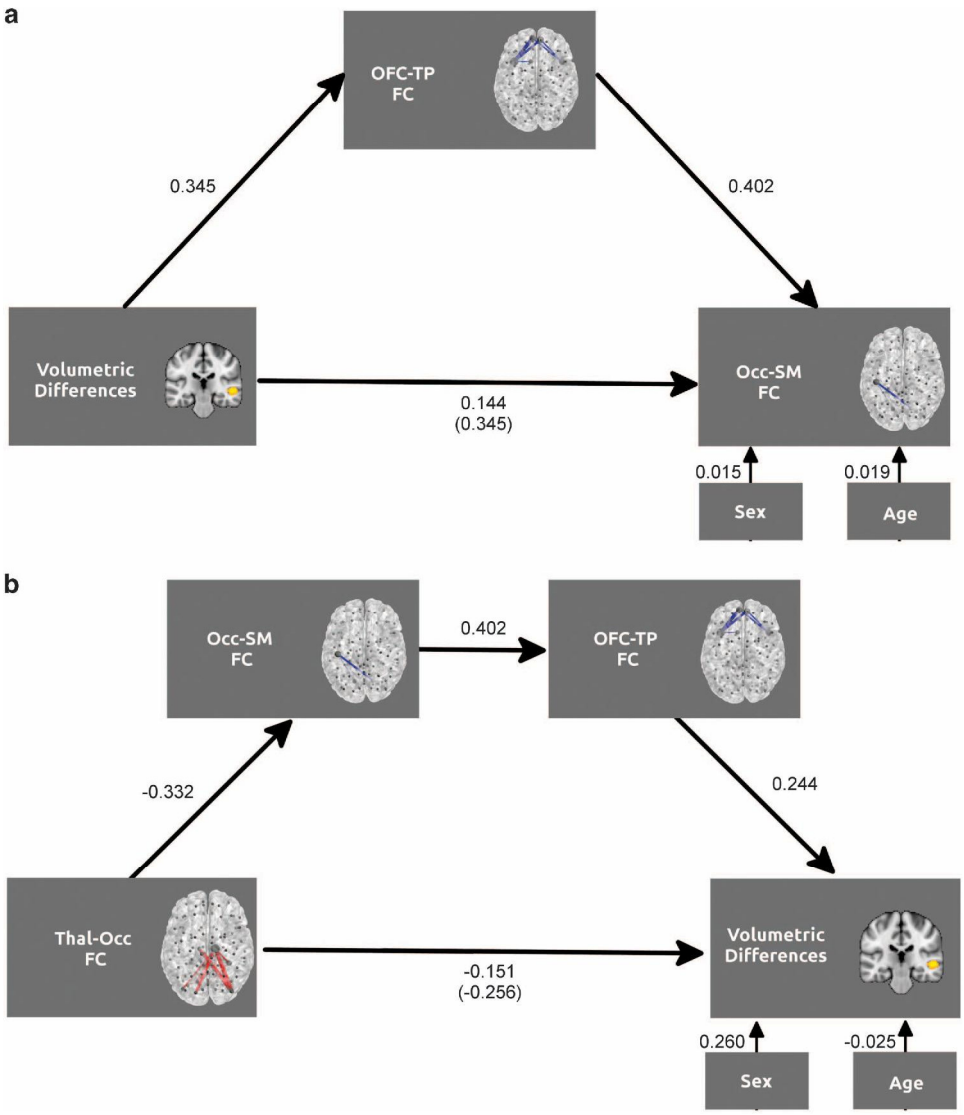

Figure 4. Mediation models. (**a**) Mediator effects of the orbitofrontal-temporal pole subnetwork (OFC-TP) on the association between volumetric differences within the superior temporal sulcus (STS) and the mean functional connectivity (FC) of the occipito-sensorimotor subnetwork (Occ-SM); (**b**) mediator effects of the occipito-sensorimotor (Occ-SM) and orbitofrontal-temporal pole (OFC-TP) subnetworks on the association between the mean FC of the thalamic-occipital subnetwork (Thal-Occ) and volumetric differences. Both models revealed significant indirect effects between independent and dependent variables, controlling for confounding factors (sex and age). Values next to each arrow represent standardized coefficients. Values in parenthesis correspond to standardized coefficients when the effects of mediator variables are removed.

within the STS (model 2). According to these results, two distinct hypotheses are proposed.

Hypothesis 1: *Direct and indirect contributions of volumetric alterations to a decreased connectivity between the STS and the OFC, and between the OFC and posterior regions, respectively.*

The results from the mediation model revealed that the association between structural findings and the mean FC of the Occ-SM subnetwork was significantly mediated by the mean FC of the OFC-TP subnetwork. One possible explanation of this mediation effect relies on the hypothesis that the structural reductions of the STS may contribute to a diminished number of tracts of the arcuate fasciculus (one subcomponent of the superior longitudinal fasciculus (SLF), connecting regions from the temporal lobe to frontal areas) in OCD patients. Consequently, this may contribute to a diminishment of the projections between the OFC and limbic areas (for example, the temporal pole, through the uncinate fasciculus), contributing to an impaired behavioral and emotional regulation. In turn, projections from the OFC to occipital brain regions (for example, the lingual gyri), and to posterior brain regions (through another subcomponent of the SLF) may in turn be diminished.

Hypothesis 2: *Hyperconnectivity between thalamic-cortical projections has an impact on volumetric reductions on the superior temporal sulcus mediated by abnormal FC involving posterior and anterior regions.*

Another alternative hypothesis, which follows an inverse path of the one proposed in the first hypothesis, suggests that volumetric alterations are a consequence rather than a cause of FC alterations. We have previously discussed that the Thal-Occ network may represent the aberrant CSTC loops typically described in OCD patients. This network is significantly associated with the remaining observed structural and functional between-

group differences. Nevertheless, it was found that the association between this network and volumetric differences was significantly mediated by both subnetworks with decreased FC in OCD patients. In this context, one may hypothesize that the hyperconnectivity of the loops projecting from the thalamus to parietal and occipital cortical regions may have an impact on the occipito-sensorimotor connectivity. Projections from these regions to orbitofrontal regions, through the SLF, may disturb the functioning of the OFC and its synchrony with limbic regions and the temporal pole (linked via the uncinate fasciculus). An impaired feedback between these regions may, in turn, result in an impaired structural connectivity between the OFC and the STS (throughout the arcuate fasciculus), which may ultimately cause volumetric reductions in this area.

Strengths and limitations

It is worth to acknowledge some strengths and limitations associated with this work. The first strength is associated with the multimodal approach here implemented. With this, we could provide complementary evidence for abnormal structural and functional brain patterns in OCD patients and how they can be integrated to understand the neural mechanisms associated with the disorder. In addition, the group differences were identified using very conservative approaches, with restrict thresholds for assessing both volumetric (with non-parametric permutation testing) and whole-brain ($P < 0.001$ and $P < 0.0001$) differences. Thus, considering the recent debate associated with the problem of false-positive findings in neuroimaging experiments, this conservative strategy enables an additional level of confidence in the reported findings.

On the other hand, it is relevant to highlight that the network with increases in FC (the Thal-Occ network) was identified with marginally significant results. Thus, these results need to be interpreted with additional caution. Other limitations pertain to the characteristics of the sample. One aspect relies on the fact that our sample was under medication. Recent reports have demonstrated that specific FC alterations stabilize after pharmacological intervention in OCD patients.[27] Consequently, it is reasonable to speculate that the pharmacological treatment could ameliorate the differences herein obtained. Nevertheless, it is important to mention that the duration of medication was not associated with the magnitude of the differences between OCD and HC groups, considering either the structural and functional alterations here described (data not shown). Another important issue pertains to the high heterogeneity observed among OCD patients. It is also important to highlight that the hypotheses raised with this work strongly rely on structural connections between particular brain regions. Thus, our theoretical model could be better sustained with the complementary characterization with diffusion tractography approaches.

CONCLUSIONS

In sum, we could detect a variety of functional and structural brain alterations in OCD patients. Using this multimodal approach, we could integrate these results in an integrated, theoretical model that may provide useful insights associated with the pathophysiology of the disorder. In addition, our results reinforce the importance of extending the CSTC model to fully understand the pathophysiology of the disease.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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DISCLAIMER

The paper has not been published previously, or is under consideration for publication elsewhere, in English or in any other language.

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Supplementary Information accompanies the paper on the *Translational Psychiatry* website (http://www.nature.com/tp)

Supplementary Information

MRI acquisition details

For the structural analysis, a T1 3D MPRAGE (magnetization prepared rapid gradient echo) scan was performed with the following parameters: 176 sagittal slices, repetition-time (TR) = 2730, echo-time (TE) = 3.48 ms, slice thickness = 1 mm, slice gap = 0 mm, voxel size = 1x1 mm^2, field-of-view (FoV) = 256×256 mm, flip angle (FA) = 7°. Functional MRI images were collected axially using an echo-planar imaging (EPI) sequence with blood-oxygen-level-dependent (BOLD) contrast. The acquisition parameters were: 30 slices, TR = 2000 ms, TE = 30 ms, slice thickness= 3.5 mm, slice gap = 0.48 mm, voxel size = 3.5 x 3.5 mm^2, FoV = 224×224 mm, FA = 90° and 180 volumes, total acquisition time = 6 minutes. During the resting-state scan the subjects were instructed to remain still, awake, with their eyes closed, as motionless as possible and to think of nothing in particular. None of the participants fell asleep during the acquisition. Comfortable foam padding was used to reduce head motion during the acquisition.

Voxel-based Morphometry Pipeline

Firstly, images were skull-striped and segmented into grey-matter (GM), white matter (WM) and cerebrospinal fluid (CSF) tissue classes. Afterwards, the GM images affine-registered to the Montreal Neurological Institute (MNI) standard space and averaged. This averaged image was then flipped and averaged with the non-flipped version in order to create an initial template. Then, the native GM images were non-linearly registered to this template, averaged, flipped and re-averaged to create the final study-specific symmetric GM template (Andersson, Jenkinson, & Smith, 2007). Secondly, the native GM images are non-linearly registered to the study specific template and smoothed with a Gaussian kernel with sigma = 3 mm (corresponding to FWHM = 7 mm).

Preprocessing of fMRI data

The initial five volumes of the rs-fMRI scans were discarded to reduce possible effects of magnetic field inhomogeneity at the beginning of the acquisition. After slice timing correction and removal of motion outliers, images were non-linearly normalized to the MNI standard space, using an indirect pipeline, which included: co-registration of the mean functional image to the structural scan using a rigid body transformation; nonlinear normalization of the structural scan to the MNI 152 T1 template; nonlinear registration of the functional scans to MNI standard space through the combination of the rigid-body co-registration matrix; and warp of the nonlinear transformation and resampling to 2x2x2 mm^3 voxel size.

Table S1. Descriptive statistics, correlations (above the diagonal), and variance/covariance (diagonal and below, in light grey) matrix

	STS volume	Thal-Occ FC	OFC-TP FC	Occ-SM FC
STS volume	.005	-.262*	.331**	.261*
Thal-Occ FC	-.006	.105	-.276*	-.329**
OFC-TP FC	.007	-.026	.086	.445**
Occ-SM FC	.007	-.038	.047	.128

*p<.05; **p<.001

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CHAPTER 2.2

The resting-brain of Obsessive-Compulsive Disorder

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Submitted

The resting-brain of Obsessive-Compulsive Disorder

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Running title: Intrinsic brain patterns and risky decision-making in OCD

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Abstract

Obsessive Compulsive Disorder (OCD) is one of the most debilitating psychiatric conditions, having a dramatic impact on patients' daily living. In this work, we aimed to explore behavioral and intrinsic structural and functional brain patterns of risky decision-making in OCD individuals to better understand this disease. Eighty individuals performed a resting state fMRI protocol. An independent component analysis was performed for the identification of resting-state networks. OCD patients displayed reduced functional connectivity (FC) in visual and sensorimotor networks. In addition, patients displayed altered FC between sensory networks and between default-mode and cerebellar networks.

Background

Obsessive-Compulsive Disorder (OCD) is a psychiatric condition characterized by the presence of obsessive thoughts and compulsions. It has an estimated prevalence of 2-3% and constitutes one of the most debilitating psychiatric disorders with a severe impact on patients' daily life (Karno, Golding, Sorenson, & Burnam, 1988). While OCD patients are typically aware of the nonsensical nature of their obsessions and compulsions, they are not able to control these symptoms (Graybiel & Rauch, 2000). Neurobiologically, OCD is thought to be characterized by an abnormal functioning within cortico-striato-thalamo-cortical (CTSC) loops.

Meta-analytic aggregations of neuroimaging studies suggest that OCD is characterized by marked neurobiological alterations in structural and functional modalities. Structurally, OCD is characterized by consistent volumetric grey matter volume (GMV) alterations, including increases in the left postcentral gyrus, middle frontal, putamen, thalamus and culmen while displaying decreased GMV in occipital regions in temporal and insular regions (Eng, Sim, & Chen, 2015). During executive function tasks – a domain which has been acknowledged to be severely compromised in OCD (Menzies et al., 2007) – is associated with several altered patterns of brain activation of the cerebellum, putamen, parahippocampus, postecentral gyrus, parietal cortex, inferior, medial and superior frontal nodes, cingulate, as well as the caudate (Eng et al., 2015). More recently, it has been also highlighted that OCD patients present consistent patterns of increased brain activity during emotional processing of the amygdala, putamen, orbitofrontal cortex (OFC), inferior occipital cortex and middle temporal gyrus (Thorsen et al., 2018).

Regarding resting-state fMRI studies, the literature has demonstrated altered functional connectivity (FC) within the default-mode network (DMN) (Jang et al., 2010; Koçak, Kale, & Çiçek, 2012), between the fronto-parietal network (FPN) and DMN (Stern, Fitzgerald, Welsh, Abelson, & Taylor, 2012), increased amplitude of low-frequency fluctuation (ALFF) in the OFC, anterior cingulate cortex (ACC) and reduced ALFF in cerebellum and parietal cortex (J. Hou et al., 2012), as well as increased striatal-OFC FC (Jung et al., 2013). In addition, reports of whole-brain FC have been published, indicating increased FC between nodes of the CTSC and reduced FC in the cerebellum, as well as in occipital and temporal cortices (J.-M. Hou et al., 2014; Moreira et al., 2017).

Despite the cumulative evidence regarding the characterization of task-related patterns of brain activation and the patterns of resting-state FC, a model-free characterization of the resting-state FC among different resting-state networks is quite underexplored. In this context, with this work, we aimed to characterize the patterns of within and between resting-state networks' functional connectivity, using an Independent Component Analysis (ICA) approach.

Methods and Materials

Participants

Forty OCD patients and 40 healthy controls (matched for sex, age and education) participated in this study. All participants were right-handed and had no history of neurological or comorbid disorders. OCD patients (all receiving medication) were characterized with a comprehensive clinical assessment. A semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-TR and the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS, (Goodman et al., 1989)) were administered to establish the OCD diagnosis. Anxiety and depression levels were assessed using the Hamilton Anxiety (HAM-A) and Hamilton Depression (HAM-D) scales, respectively. The sample characterization is presented on Table 1. The study was conducted according to the Declaration of Helsinki principles and was approved by the Ethics Committee of Hospital de Braga (Portugal). The study goals were explained, and written informed consent was obtained from each participant. Imaging was performed using a clinical approved 1.5 T Siemens Magnetom Avanto MRI Scanner (Siemens, Erlangen, Germany). The acquisition and preprocessing parameters of structural and functional MRI sequences are detailed in File S1.

Independent Component Analysis and identification of resting-state networks

Resting-state network (RSN) maps were analyzed voxel-wise through a probabilistic independent component analysis (PICA) as implemented in Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC), distributed with FSL

(Beckmann & Smith, 2004). PICA is a fully data-driven approach that enables the isolation of components based on the temporal correlation of the corresponding areas, while maximizing the spatial independence between components. Dual-regression analysis was performed to estimate the subject-specific components that correspond to the group-wise RSNs. Because the PICA approach may identify noisy components corresponding to non-biological signal, such as movement artifacts, the independent components were selected after visual inspection of their spatial distribution (Horowitz-Kraus, DiFrancesco, Kay, Wang, & Holland, 2015). Specifically, components that were mainly present in regions that do not generate the blood-oxygen-level-dependent (BOLD) signal (white matter, ventricles or outside the brain) were excluded from the analysis.

Statistical analysis

Statistical group comparisons were conducted using two-samples t-tests, adjusted for confounding factors (sex and age). Intra-RSN FC was compared between groups, using a non-parametric permutation procedure implemented in the randomize tool from FSL (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Threshold-free cluster enhancement (TFCE) was used to detect widespread significant differences and control the family-wise error rate (FWE-R) at α=.05. Each contrast underwent 5.000 permutations. For the analysis of inter-RSN FC, the time-series of each RSN were extracted and using the Fisher's Z-transformed Pearson correlation coefficients, matrices of functional connectivity between pairs of RSNs were created. Individual correlations were statistically compared (α=.05 with FDR correction) between groups.

Results

Twenty-two components were obtained from the PICA. Fifteen of these components were found to be representative of the most typical RSNs (Figure 1a). OCD patients displayed reduced FC within the primary visual (PVN), high visual (HVN) and sensorimotor (SMN) networks (Supplementary Information). Specifically, for the PVN, there were significant differences between groups in one large cluster (2465 voxels), with peaks on the left calcarine and the left

lingual gyrus (Figure 1b); for the HVN, patients had decreased FC in six clusters with peaks in distinct occipital subdivisions (Figure 1c); for the SMN, OCD patients had significantly decreased FC in one cluster comprising the paracentral and the supplementary motor area of the left hemisphere (Figure 1d).

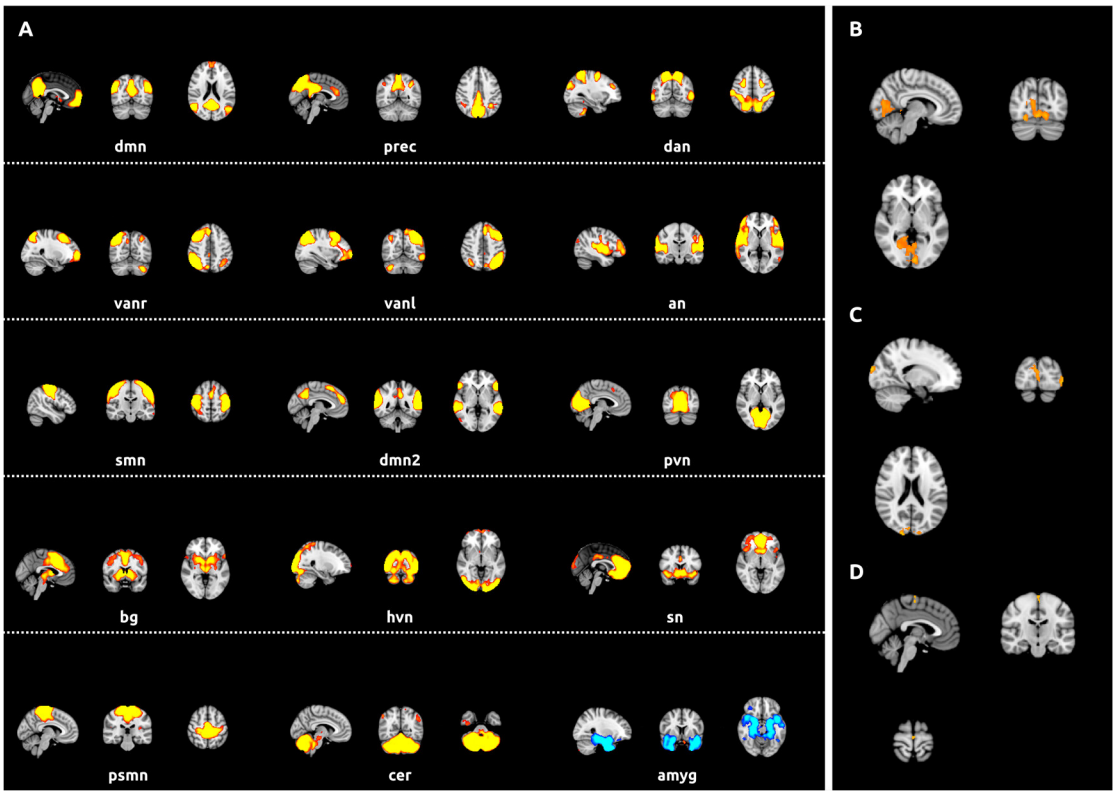

Figure 1. Resting state networks. (A) Resting state networks identified through ICA. Group ICA maps thresholded at Z> 3.09 (dmn, default mode network; prec, precuneus network; dan, dorsal attention network; vanr, ventral attention network – right; vanl, ventral attention network – left; an, auditory network; smn, sensorimotor network; dmn2, default mode network – 2nd component; pvn, primary visual network; bg, basal ganglia network; sn, salience network; psmn, primary sensorimotor network; cer, cerebellar network; amyg; amygdala network); (B) group differences within the primary visual network; (C) group differences within the high visual network; (D) group differences within the sensorimotor network.

Regarding the inter-RSN FC, despite the fact that several patterns of altered FC between distinct RSNs were observed in OCD patients (as graphically displayed in Supplementary Information), the only finding remaining statistically significant after correction for multiple

comparisons (bold lines) was a reduction in the association between PVN and one SMN in OCD patients ($t_{(79)}$=5.73, p<.001) and an increase of the association between a component of the DMN and the cerebellar network. The patterns of altered FC between different RSNs in OCD patients are graphically displayed on Figure 3.

Discussion

In this work, we aimed to characterize the patterns of resting-state FC within and between different resting-state networks. We observed that OCD patients are characterized by altered FC patterns of distinct RSNs, particularly in visual and sensorimotor networks. Patients were also characterized by a complex profile of connectivity between distinct resting-state networks.

Our study demonstrated a significantly reduced FC within the visual network in OCD patients, which complements our previous findings of altered brain FC within occipital regions (Moreira et al., 2017). The involvement of sensorial-related deficits has been highlighted to play a crucial role in several psychiatric conditions, including maniac and depressed groups of patients with bipolar disorder (Shaffer et al., 2018).

These results are in accordance with the hypothesis that one of the mechanisms underlying the OCD phenotype relies on the deactivation of occipital/parietal regions which are associated with the visual-perceptual processing of incoming rich stimuli (Gonçalves, Marques, Lori, Sampaio, & Branco, 2010). Previous research has highlighted that the visual network is involved on the allocation of attentional (particularly, visual) resources, such that an increased FC within this network is thought to reflect a greater demand on the allocation of resources (Horowitz-Kraus et al., 2015). In addition, the activity of these regions was previously associated with the generation of somatic arousal, possibly indicating that modulation through arousal is adaptive in order to promote an easier processing of relevant visual information (Gauthier, Anderson, Tarr, Skudlarski, & Gore, 1997).

One note to highlight that our sample of OCD patients was under medication. As such, it is plausible that the medication may influence behavioral patterns of risky decision-making,

and even the intrinsic structural and functional connectivity patterns, in these patients. Future studies assessing drug-naïve OCD patients are needed to tackle this confounding effect.

In sum, our study offers evidence for the involvement of altered sensorial-related patterns of brain FC, which may be underline distinct mood states, as suggested in other psychiatric conditions (Shaffer et al., 2018).

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Disclosures

The authors have no conflict of interest to disclose. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The paper has not been published previously, or is under consideration for publication elsewhere, in English or in any other language.

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Supplementary Information

MRI data acquisition

Imaging was performed at Hospital de Braga using a clinically approved 1.5 T Siemens Magnetom Avanto TIM-system MRI scanner (Siemens, Erlangen, Germany) equipped with a standard 12 channel receive-only head coil.

For the structural analysis, a T1 3D MPRAGE (magnetization prepared rapid gradient echo) scan was performed with the following parameters: 176 sagital slices, repetition-time (TR) = 2730, echo-time (TE) = 3.48 ms, slice thickness = 1 mm, slice gap = 0 mm, voxel size = 1x1 mm2, field-of-view (FoV) = 256×256 mm, flip angle (FA) = 7°.

Functional images were collected axially using an echo-planar imaging (EPI) sequence sensitive to the blood-oxygen-level-dependent (BOLD) contrast. The acquisition parameters were: 30 slices, TR = 2000 ms, TE = 30 ms, slice thickness= 3.5 mm, slice gap = 0.48 mm, voxel size = 3.5 x 3.5 mm2 FoV = 1344×1344 mm, FA = 90° and 180 volumes.

During the resting state scan the subjects were instructed to remain still, awake, with their eyes closed, as motionless as possible and to think of nothing in particular. None of the participants fell asleep during the acquisition. Foam pads were used in both head sides in order to reduce head motion during the acquisition.

Data processing

Rs-fMRI data was processed using a probabilistic independent component analysis (PICA) as implemented in MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components), a program distributed by FSL (Beckmann and Smith 2004). PICA is a fully data-driven approach that enables the users to isolate components based on the temporal correlation of the corresponding areas, while maximizing independence between the components.

The subjects' datasets were temporally concatenated, thus forming a single 4D dataset. This dataset was then used to estimate group-wise RSN with MELODIC. The software automatically estimated the number of components for extractionwas automatically estimated without specifying the number of independent components to extract.

Dual-regression analysis was performed to estimate the subject-specific components that correspond to the group-wise RNS's. The resulting components were then visually inspected. The components were selected for analysis when they presented activations in gray matter. From these components we excluded those that overlapped with vascular regions and those that resulted from artifacts such as head motion.

The RSNs' time series from each individual were initially extracted to study inter-RSNs functional connectivity alterations. The correlations between pairs of time-courses were then estimated using the "glmfit" function from Matlab. The obtained correlation coefficients were transformed to Z-scores using Fisher's r to z transformation. Z values were used as inputs in two-sample t-tests to test for group differences. Results were considered significant at $p<.005$ given the large amount of comparisons.

Sample characteristics

The descriptive statistics for both groups are presented on Table S1. As represented, there were no statistically significant between-group differences with regards to age, sex and education level. All the patients were receiving pharmacological interventions (72.2% were receiving selective serotonin reuptake inhibitors, 11.1% were receiving tricyclic antidepressants and 16.7% were receiving combined medication). There were no significant between-group differences in the number of motion spikes during the EPI acquisition.

Table S1. Socio-demographic and clinical characteristics of patients with obsessive-compulsive disorder and healthy comparison subjects

Characteristic	OCD (n=40)	HC (n=40)	Difference
Age, Years	26.52 ± 6.55	26.45 ± 5.39	ns
Education, Years	13.48 ± 2.20	14.63 ± 3.20	ns
Sex, n (%) Males	13 (32.5%)	13 (32.5%)	ns
Y-BOCS, Total Score	24.55 ± 6.75	–	–
Y-BOCS, Obsessions	13.18 ± 3.71	–	–
Y-BOCS, Compulsions	11.38 ± 3.54	–	–
HAM-A-, Total Score	4.83 ± 4.16	–	–
HAM-D-, Total Score	5.88 ± 4.65	–	–
Medication			
% SSRI	72.2%	–	–
% TCA	11.1%	–	–
% combined	16.7%	–	–
Motion Spikes	8.10 ± 4.91	6.35 ± 3.32	ns

Values are presented as mean ± SD. Y-BOCS, Yale-Brown Obsessive Compulsive; HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale; SSRI, Selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants. Spikes are volumes with high motion, discarded while estimating connectivity patterns.

Table S2. Group differences between within resting-state networks

Network	Voxels	T-score	x	y	z	Region
PVN						
	2465	4.12	-6	-86	-2	Calcarine_L
		4.03	0	-72	-8	Vermis_6
		3.94	-10	-80	-10	Lingual_L
HVN						
	287	4.26	18	-98	20	Occipital_Sup_R
		3.67	0	-90	14	Calcarine_L
		3.66	2	-90	6	Calcarine_L
	82	4.07	-42	-90	-6	Occipital_Inf_L
		3.35	-44	-88	4	Occipital_Mid_L
	60	2.95	-12	-96	20	Occipital_Sup_L
		2.76	-12	-94	28	Cuneus_L
		2.65	-8	-90	30	Cuneus_L
	48	3.73	-22	-104	-4	Occipital_Mid_L
	11	3.28	-34	-98	-2	Occipital_Mid_L
	3	3.02	-42	-78	-14	Occipital_Inf_L
SMN						
	30	3.76	0	-16	70	Paracentral_L
		3.59	-2	-18	62	Supp_Motor_Area_L

PVN, Primary Visual Network; HVN, High Visual Network; SMN, Sensorimotor Network

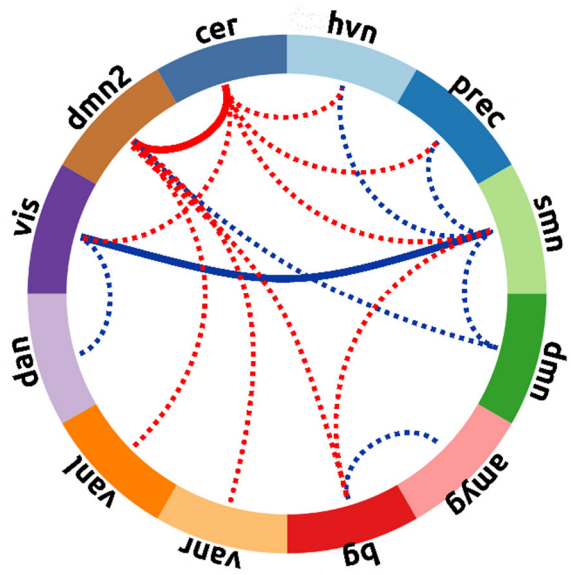

Figure S1. Group differences between resting-state networks. Dashed and bold lines represent uncorrected and corrected for multiple-comparisons differences (red lines: associations significantly increased in the OCD group; blue lines: associations significantly reduced in the OCD group).

CHAPTER 2.3

Dissociation between striatal volume and risky decision-making in OCD

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Submitted

Dissociation between striatal volume and risky decision-making in OCD

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Running title: Intrinsic brain patterns and risky decision-making in OCD

Keywords: obsessive-compulsive disorder, resting-state networks, fMRI, decision-making, risk-taking

Abstract

Impaired decision-making has been proposed as one of the core behavioral manifestations of the Obsessive-Compulsive Disorder (OCD). Here, we explored the association between structural brain patterns and risky decision-making in OCD. Eighty individuals underwent structural Magnetic Resonance Imaging. Risk-taking attitude was assessed during a risky decision-making task. Healthy controls displayed a positive association between the volume of striatal regions and risk taking, whereas this pattern was absent in OCD patients. The lack of a normal structure-behavior relationship between striatal volume and risky choices in OCD patients may be a structural marker of aberrant basal ganglia function in this psychiatric condition.

Background

Decision-making involves the ability of selecting among different alternatives to produce different outcomes (Lee, 2013) and constitutes a crucial aspect for individuals' daily life. The study of these processes has been progressively established as a tool for characterizing the neurobiological mechanisms of distinct neuropsychiatric disorders. It has been proposed that alterations in decision-making may be the underlying cause of obsessive-compulsive disorder (OCD), as demonstrated by behavioral and neurobiological alterations in risky decision-making (Cavedini, Gorini, & Bellodi, 2006).

Previous studies have proposed that OCD is characterized by an increased loss-aversion and that these patients present altered neurobiological responses during gambling tasks (Admon et al., 2012). However, given that task-related studies may be limited by the fact that brain activation is likely to be related with individuals' effort or strategy, examining the relationship between the structure of brain regions and behavioral profiles may yield additional important evidence. Such approach has been previously used to demonstrate that the association between structural patterns and risk-taking tendencies in healthy individuals, is dependent on the structure of the insula and striatal regions (Cox et al., 2010). Nevertheless, there has been a limited use of this strategy to establish the link between intrinsic brain signatures and risk-taking in psychiatric conditions. To the best of our knowledge, no study has tested yet the relationship between the structure of brain regions and risk in OCD.

Given that the striatum is a key component of the most widely accepted models of OCD, playing a crucial role on the pathophysiology of the disorder (interfering with an under-reliance on goal-directed behavior), and the fact that these regions are consistently activated in tasks associated with risk [see the meta-analytic map obtained with Neurosynth (Figure 1A)] – we focused on characterizing the association between the volume of striatal regions and risk in OCD patients.

Method and Results

Thirty-nine medicated OCD patients [27 females; mean age=26.6 years, total scores of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) ranging from 11 to 35 (M = 24.93, SD = 5.69)]) and 39 healthy controls (HC, 26 females, mean age=26.4 years), with no history of neurological or comorbid disorders, participated in this study. All individuals were right-handed and provided written informed consent. A T1-weighted scan was acquired to assess brain structure. The volumes of the regions of interest (caudate, putamen and nucleus accumbens) were quantified following the brain segmentation, using a semi-automated pipeline with FreeSurfer (Fischl, 2012) (see Supplementary Information for a detailed description). Participants were then involved in an experimental apparatus comprised of a gambling task – whose psychometric properties have been previously demonstrated (Macoveanu et al., 2013) – in which they were had to choose between two decks of cards displayed face down. The "ace of hearts" was hidden in one of these decks. Participants had to guess the deck containing this card to receive a reward; or, otherwise, lose the bet. Each scenario was composed by seven cards, presented according to six risk levels (range of probability: 1/7 to 6/7) (Figure 1B). The task was presented as an even distribution of choices across all risk levels in two sessions with a one-minute interval.

Moderation analyses were conducted to assess the impact of group on the association between striatal volume and risk. The proportion of 1/7 choices (quantification of risk-taking) and was defined as the dependent variable and group as the moderator variable. To reduce the number of comparisons, a second-order latent variable was defined in a reflective model with the different striatal regions being defined as manifest variables. The second-order latent variable striatum was defined as the independent variable in an initial moderation model. There were significant moderation effects of group on the association between the latent variable striatum and risk ($F_{(3,74)}$=3.18, p=.029, R2=.11) – HC displayed a significant positive association between volume and the proportion of high-risk choices (Figure 1D), whereas this association was absent in the OCD group.

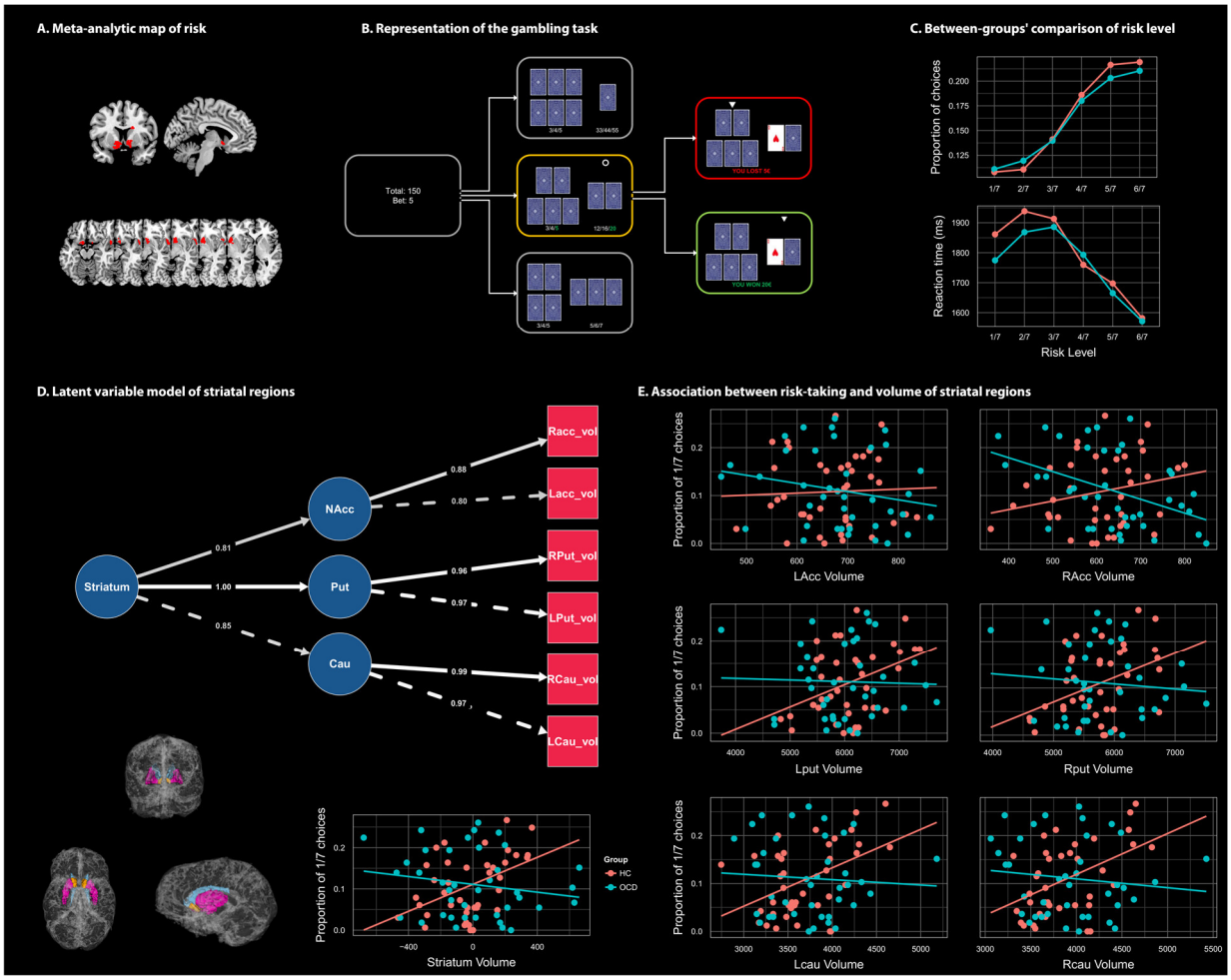

Figure 1. Risky decision-making and striatal volume. A: Meta-analytic map representing the automated aggregation of fMRI studies involving the term "risk", obtained with Neurosynth. B: Overview of the gambling task: Participants were informed about the amount of accumulated money and the value of the current bet; next, two decks were displayed facedown; finally, the location of the ace of arts was displayed and the subjects received the feedback. C: Between-groups' comparison of proportion of choices (top) and reaction-times (bottom) for different risk levels. D: Latent variable model comprising the volume of different bilateral striatal regions. Manifest variables (squares) correspond to each volume; latent variables are represented in circles. Bottom: moderation effect of group on the association between the volume of the latent variable "striatum" and proportion of high-risk choices. E: Decomposition of the global moderation effect for each striatal region.

Given the existence of statistically significant effects on the moderation model with the latent variable, individual moderation effects were tested by assessing the impact of group on the association between each manifest variable and risk-taking. Significant uncorrected moderator effects of group were observed for right putamen ($F_{(3,74)}$=3.50, p=.020, R2=.12), left ($F_{(3,74)}$=2.76, p=.048, R2=.10) and right caudate ($F_{(3,74)}$=3.17, p=.030, R2=.12) – HC had positive, significant

associations between the volume of these regions and the number of 1/7 choices (range of correlation coefficients: .375-.475) (Figure 1E). For the OCD group, these associations were observed in the negative direction, although non-statistically significant. Considering the individual manifest variables, significant moderator effects of group were observed for right putamen ($F_{(3,74)}$=3.50, p=.020, R2=.12), left ($F_{(3,74)}$=2.76, p=.048, R2=.10) and right caudate ($F_{(3,74)}$=3.17, p=.030, R2=.12), with healthy controls displaying positive, significant associations between the volume of these regions and the number of 1/7 choices (range of correlation coefficients: .375-.475) (Figure 1E). For the OCD group, the associations between these volumes and choices on the highest risk condition are observed in the negative direction, although non-statistically significant.

Discussion

In this work, we explored the association between risky decision-making with volumetric brain patterns in OCD patients. Even though the patterns of risk were similar between groups, it had distinct associations with striatal volume between OCD patients and HC. Risk was dependent on the structure of ventral and dorsal striatal regions in HC, such that increased volume of these regions is linked to the number of high-risk choices. In contrast, OCD patients displayed a null association between the volume of these regions and risk-taking.

Resting-state functional connectivity patterns of the striatum were previously associated with task-related brain activity during risk (Kohno, Morales, Ghahremani, Hellemann, & London, 2014). Neurotransmission of dopamine in the nucleus accumbens has been demonstrated to influence motivational drive (Soares-Cunha et al., 2016), highlighting the role of this brain region on expected reward (Knutson, Adams, Fong, & Hommer, 2001). The caudate and the putamen have been involved on on the encoding of specific action-outcome associations in goal-directed action and on the action-selection based on the expected reward value (Balleine, Delgado, & Hikosaka, 2007). The imbalance between the structure and function of these regions has been implicated on an a reduced reliance on goal-directed strategies, which is a core feature of OCD (Burguiere, Monteiro, Mallet, Feng, & Graybiel, 2015).

OCD patients are described to presented marked impairments in decision-making under ambiguity, but not under risk (Starcke, Tuschen-Caffier, Markowitsch, & Brand, 2010). Even though this investigation reveals that OCD patients display a risk-taking behavior equivalent to HC, the neurobiological mechanisms governing such behavior are likely to be different in this psychiatric condition. In sum, this study establishes a unique link between structural brain patterns with risky decision-making behavior, which seems to be abolished in OCD. Together, these findings may offer important insights regarding the pathophysiology of the disorder.

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Disclosures

The authors have no conflict of interest to disclose. The research was conducted in the absence of any commercial or financial relationships. The paper has not been published previously or is under consideration for publication elsewhere.

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Supplementary Information

Participants

Patients with Obsessive-Compulsive Disorder (OCD) were recruited from the psychiatric department at the Hospital of Braga (Braga, Portugal). The clinical diagnosis was established by experienced psychiatrists, based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth-Edition (DSM-IV-TR) and on the Mini-International Neuropsychiatric Interview (MINI). The severity of the disorder was assessed throughout the administration of the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS). All the patients were receiving pharmacological treatment, for at least three months, including SSRI medication (72.2%), TCA (11.1%) or combined pharmacological treatment (16.7%). Participants were recruited from the community to match the group of patients, according to sex, age and education level.

MRI data acquisition

A T1-weighted MPRAGE (magnetization prepared rapid gradient echo; 176 sagittal slices, repetition-time =2730 ms, echo-time=3.48 ms, slice thickness = 1 mm, slice gap = 0 mm, voxel size = 1x1x1 mm, field-of-view = 256×256 mm, flip angle = 7°) was acquired in a 1.5 T Siemens Magnetom Avanto Scanner, equipped with a standard 12 channel receive-only head coil. The imaging session as performed at the Hospital of Braga (Braga, Portugal).

Before any data processing and analysis, all the acquisitions were visually inspected to confirm that artifacts such as head motion did not critically affect them and that participants had no gross anatomical abnormalities. For the volumetric analysis, we used a semi-automated brain segmentation implemented with the Freesurfer software (version 4.5.0, Fischl et al., 1999). The preprocessing was conducted following the recommended pipeline available at (http://surfer.nmr.mgh.harvard.edu/). The bilateral volumes of the caudate, putamen and nucleus accumbens were defined according to a standard subcortical atlas (Fischl et al., 2002).

Data analysis

The latent variable model was defined to derive a higher-order variable, reflecting the volumes of striatal regions. The reasoning behind this strategy relies on the fact that due to the high correlation between these brain regions, one can minimize the problem of multiple comparisons, by assessing a global variable that integrates information for all the individual brain regions. This second-order latent variable was reflected on three first-order latent variables corresponding to bilateral regions, which in turn was reflected in each unilateral brain volume – here defined as an individual manifest variable.

The use of moderation analysis allows the determination of whether the effect of some putative causal variable X on outcome Y depends in one way or another on a moderator variable. This analysis estimates a moderation model with a single moderator (Group) of the effect of *striatum* on risk-taking (by Group). The omnibus statistical significance was assessed to test the null hypothesis of non-significant effects of the global model.

Moderation analysis were implemented in the PROCESS Macro for SPSS (Bolin, 2014). The remaining statistical analyses, including the latent variable model and descriptive statistics were implemented in R Studio, with the *Lavaan* (Rosseel, 2012) and *base* packages (R Core Team, 2013), respectively.

Results

The descriptive statistics for the volume of each striatal region by group are summarized on Table S1 and graphically represented on Figure S1. There were no statistically significant between-group differences regarding any striatal region.

The model for the global variable *striatum* yielded statistically significant effects ($F_{(3,74)}$=3.18, p=.029). The interaction between volume and risk was a significant predictor in this model (Table S2). The moderator had a statistically significant effect on the dependent variable ($F_{(1,74)}$=9.14, p=.003), accounting for 10.9% of its variance (R^2=.109) (Table S3).

Table S1: Descriptive Statistics of each striatal volume, by group

	HC				OCD				t-test
	Mean	**SD**	**Sk**	**K**	**Mean**	**SD**	**Sk**	**K**	
LCau	3690.96	424.01	0.34	-0.43	3741.19	469.07	0.45	0.36	$t_{(76)}$=-0.50, p=.621
RCau	3870.24	415.06	0.63	-0.63	3936.51	519.56	0.45	-0.02	$t_{(76)}$=-0.62, p=.536
LPut	6073.23	620.77	0.22	-0.53	5980.52	773.58	-0.24	0.65	$t_{(76)}$=0.58, p=.561
RPut	5724.57	581.67	0	-0.69	5768.96	717.78	0.24	0.18	$t_{(76)}$=-0.30, p=.765
LNacc	670.83	81.75	-0.17	-0.63	683.82	99.59	-0.41	-0.29	$t_{(76)}$=-0.63, p=.531
RNacc	608.22	99.72	-0.35	-0.29	635.09	117.44	-0.14	-0.55	$t_{(76)}$=-1.1, p=.280

Sk – Skewness; K – Kurtosis; LCau – Left Caudate, RCau – Right Caudate, LPut – Left Putamen, RPut – Right Putamen, LNacc – Left Nucleus Accumbens, RNacc – Right Nucleus Accumbens.

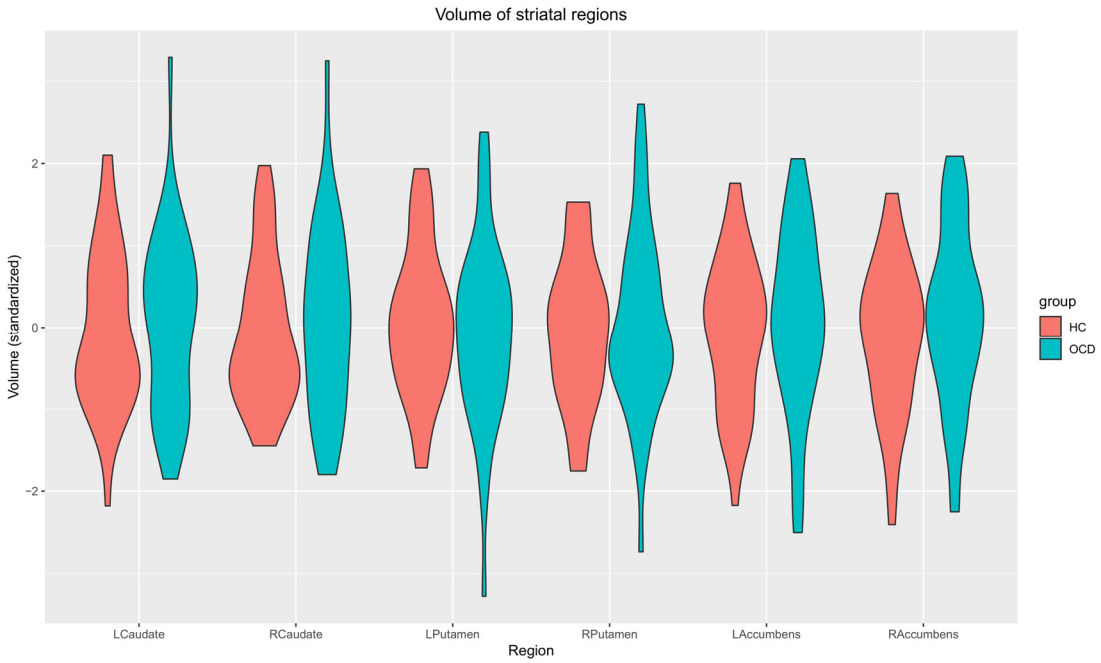

Figure S1: Violin plots representing Between-groups' comparisons on different striatal regions. The x-axis represents each brain region; the y-axis corresponds to the standardized brain volume of each structure.

Given that this global model yielded statistically significant moderator effects, we next decomposed the global interaction by assessing the statistical significance of each individual striatal volume. It was noted that the models corresponding to the left caudate (Model 2;

$F_{(3,74)}$=2.76, p=.048), right caudate (Model 3; $F_{(3,74)}$=3.17, p=.029) and right accumbens (Model 7; $F_{(3,74)}$=3.50, p=.020) yielded statistical significance at the omnibus level.

Table S2: Effects of individual predictors on risk-taking

Model	Variable	B	SE	t	p	LLCI	ULCI
Model 1	constant	0.1111	0.0118	9.403	0	0.0875	0.1346
Global	Striatum	0.0002	0.0001	2.8425	0.0058	0	0.0003
	Group	-0.0001	0.0167	-0.007	0.9945	-0.0333	0.0331
	Striatum*Group	-0.0002	0.0001	-3.0232	0.0034	-0.0003	-0.0001
Model 2	constant	-0.1886	0.1052	-1.7923	0.0772	-0.3982	0.0211
LCau	LCau	0.0001	0	2.8368	0.0059	0	0.0001
	Group	0.3413	0.1428	2.3904	0.0194	0.0568	0.6258
	LCau*Group	-0.0001	0	-2.3969	0.0191	-0.0002	0
Model 3	constant	-0.2222	0.1118	-1.9881	0.0505	-0.4449	0.0005
RCau	RCau	0.0001	0	2.9709	0.004	0	0.0001
	Group	0.4061	0.1442	2.8165	0.0062	0.1188	0.6934
	RCau*Group	-0.0001	0	-2.8251	0.0061	-0.0002	0
Model 4	constant	-0.1838	0.1197	-1.5354	0.1289	-0.4223	0.0547
LPut	LPut	0	0	2.4501	0.0166	0	0.0001
	Group	0.3155	0.1527	2.0654	0.0424	0.0111	0.6198
	LPut*Group	-0.0001	0	-2.0487	0.044	-0.0001	0
Model 5	constant	-0.19	0.12	-1.5839	0.1175	-0.429	0.049
RPut	RPut	0.0001	0	2.4967	0.0148	0	0.0001
	Group	0.363	0.155	2.3415	0.0219	0.0541	0.6719
	RPut*Group	-0.0001	0	-2.3405	0.022	-0.0001	0
Model 6	constant	0.08	0.1033	0.7746	0.441	-0.1258	0.2858
LNacc	LNacc	0	0.0002	0.2729	0.7857	-0.0003	0.0003
	Group	0.1478	0.1349	1.0959	0.2767	-0.1209	0.4165
	LNacc*Group	-0.0002	0.0002	-1.0748	0.2859	-0.0006	0.0002
Model 7	constant	-0.0011	0.0732	-0.0144	0.9885	-0.147	0.1448
RNacc	RNacc	0.0002	0.0001	1.5089	0.1356	-0.0001	0.0004
	Group	0.2954	0.098	3.0144	0.0035	0.1001	0.4907
	RNacc*Group	-0.0005	0.0002	-3.0027	0.0036	-0.0008	-0.0002

LCau – Left Caudate, RCau – Right Caudate, LPut – Left Putamen, RPut – Right Putamen, LNacc – Left Nucleus Accumbens, RNacc – Right Nucleus Accumbens.

In addition, even though no omnibus significance was obtained for Models 4 and 5 (left and right putamen), it was noted that the moderator effect in these models produced significant highest order effects ($F_{(1,74)}$=4.20, p=.044 and ($F_{(1,74)}$=5.48, p=.022), respectively), accounting for changes in the explained variance of 5.2% and 6.8%, respectively (Table S4).

Table S3: Test of highest order unconditional interaction (moderator effects)

Model	R^2-change	F	df1	df2	p
Global Model	0.1094	9.14	1	74	0.0034
Model 2	0.0698	5.7449	1	74	0.0191
Model 3	0.0956	7.9809	1	74	0.0061
Model 4	0.0524	4.1973	1	74	0.044
Model 5	0.0679	5.4779	1	74	0.022
Model 6	0.0152	1.1553	1	74	0.2859
Model 7	0.1067	9.016	1	74	0.0036

Table S4: Conditional effects of striatal volume for each group

Model	group	Effect	se	t	p	LLCI	ULCI
Model 1	HC	0.0002	0.0001	2.8425	0.0058	0	0.0003
Global	OCD	0	0	-1.2003	0.2338	-0.0001	0
Model 2	HC	0.0001	0	2.8368	0.0059	0	0.0001
Lcau	OCD	0	0	-0.436	0.6641	-0.0001	0
Model 3	HC	0.0001	0	2.9709	0.004	0	0.0001
Rcau	OCD	0	0	-0.8073	0.4221	-0.0001	0
Model 4	HC	0	0	2.4501	0.0166	0	0.0001
Lput	OCD	0	0	-0.2202	0.8263	0	0
Model 5	HC	0.0001	0	2.4967	0.0148	0	0.0001
Rput	OCD	0	0	-0.6365	0.5264	0	0
Model 6	HC	0	0.0002	0.2729	0.7857	-0.0003	0.0003
Lacc	OCD	-0.0002	0.0001	-1.3616	0.1775	-0.0004	0.0001
Model 7	HC	0.0002	0.0001	1.5089	0.1356	-0.0001	0.0004
Racc	OCD	-0.0003	0.0001	-2.862	0.0055	-0.0005	-0.0001

CHAPTER 2.4

Altered response to risky decisions and reward in obsessive-Compulsive Disorder

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Altered response to risky decisions and reward in obsessive-Compulsive Disorder

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Running title: Functional correlates of risky decision-making in OCD

Keywords: obsessive-compulsive disorder, gambling, fMRI, decision-making, risk-taking, hot processing

Abstract

Obsessive-compulsive disorder (OCD) is characterized by the presence of ritualistic behaviors that allow the reduction, or even the neutralization, of the anxiety provoked by obsessions. This profile of excessive rumination and indecision has motivated the view of OCD as a disorder of decision-making. Most contributions addressing decision-making in OCD patients focused on cognitive aspects of decision-making. In this study, we aimed to extend the current state-of-the-art by characterizing changes in decision-making patterns during affective, or "hot" decision-making behavior in OCD patients. In a functional magnetic resonance imaging investigation, we assessed risky decision-making in a sample of 34 OCD patients and 33 sex and age matched healthy individuals. OCD patients were characterized by altered brain functioning during the anticipation and feedback periods of gambling scenarios. During risky decisions, patients had significant reduced activation in the posterior cingulum, lingual gyrus and anterior cingulate cortex (ACC); in addition, significant group*risk interactions were found within the calcarine, precuneus, amygdala and ACC. During the losses feedback, significant group-by-risk interactions involving the orbitofrontal cortex, ACC and putamen were observed, where OCD patients were characterized by hyper-reactivity to unexpected losses. These results support the idea that OCD is characterized by abnormal patterns of brain function during risky decision-making in a set of brain regions that have been consistently implicated in the processing of reward prediction errors. Together, these findings suggest that OCD patients may display alterations in affective "hot" processes implicated in decision-making behavior, which may underlie an increased indecisiveness and intolerance to uncertainty in these patients.

Background

Obsessive compulsive disorder (OCD) is a psychiatric disorder characterized by the presence of intrusive and repetitive thoughts that cause extreme levels of anxiety (obsessions) and by repetitive behaviors or mental acts overly repeated in ritualistic, stereotyped succession (compulsions) (Abramowitz, Taylor, & McKay, 2009; Graybiel & Rauch, 2000). Although OCD patients present a conscious awareness of the exaggerated nature of the ritualistic acts, these behaviors allow them to reduce/neutralize the anxiety and the negative affect related with the obsessions (Graybiel & Rauch, 2000). As such, these behavioral patterns will be continuously reinforced and will progressively be established as natural rewards (Koch et al., 2018). Depending on the severity of the disorder, these behaviors may be propagated for hours, as the OCD patient keeps facing the "what if?" question, *i.e.,* fearing that something bad may happen if he/she does not produce the ritual (Graybiel & Rauch, 2000). This uncertainty-related scheme appears to generalize to symptoms' unrelated domains, making these patients highly indecisive when choosing between simple alternatives in many real-life situations (Tolin, Abramowitz, Brigidi, & Foa, 2003). Consequently, OCD patients frequently engage in a pathological state of rumination and doubt regarding whether a particular choice was properly concluded. This has motivated the conceptualization of OCD as a disorder of decision-making (Sachdev & Malhi, 2005). Several studies have, in fact, demonstrated that OCD patients display behavioral and neurobiological alterations during decision-making performance in laboratorial settings (Cavedini, Gorini, & Bellodi, 2006; Cavedini et al., 2002). Nevertheless, previous reports have demonstrated that the contingencies of the behavioral task may selectively impact patients' performance: when the task is built on explicit and stable rules - such as the Iowa Gambling Task (IGT) - patients will display a behavioral profile similar to healthy individuals; on the other hand, when the decision-making task has implicit rules – such as the Game of Dice Task (GDT) - OCD patients are characterized by overt alterations (Starcke, Tuschen-Caffier, Markowitsch, & Brand, 2010).

The link between OCD and decision-making impairments may be better interpreted in the context of the apparent overlap between the neurobiological impairments underlying OCD and the neural mechanisms that are recruited during decision-making. Abnormal functioning within cortico-striato-thalamo-cortical (CTSC) loops have been continuously proposed as a critical pathway for the manifestation and progression of OCD symptoms both during rest and during

symptom provocation (Cavedini et al., 2006; Saxena, Brody, Schwartz, & Baxter, 1998; Ting & Feng, 2011). Meta-analytic evidence implicates several components of these loops as critical hubs for decision-making ability (Krain, Wilson, Arbuckle, Castellanos, & Milham, 2006). In fact, there is evidence of a desynchronization between fronto-limbic and fronto-striatal regions during decision-making in OCD patients (Paulus, 2007; Sachdev & Malhi, 2005). As a consequence, it has been suggested that these individuals may experience an altered processing of reward history and choice-valuation or, in other words, an altered homeostatic processing of decision-making (Paulus, 2007).

Despite the growing literature exploring the neurobiological underpinnings of decision-making in OCD patients, most contributions for the study of these processes rely on mainly cognitive or "cool", deliberative, division of decision-making processing, as approached by tasks involving ambiguity (Krain et al., 2006). In contrast, the study of "hot", affective processing, involving risky choices (Kerr & Zelazo, 2004) is still substantially underexplored in these patients. As such, with this study we aimed to add to the current state-of-the-art a comprehensive study of how OCD patients respond to risky decision-making. For this purpose, we conducted an fMRI investigation in which patients and sex and age matched healthy individuals performed a forced-choice gambling task. We aimed to characterize the behavioral profiles of risky decision-making in OCD patients, as well as the neural responses associated with the decision and feedback to different risk levels.

Methods and Materials

Participants

Sixty-seven right-handed individuals (34 OCD patients and 33 HC) without history of neurological disorders participated in this study. OCD diagnosis was established by a semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)-TR and the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS, (Goodman et al., 1989)). OCD patients were also characterized for anxiety and depression symptoms, with

Hamilton Anxiety (HAM-A) and Hamilton Depression (HAM-D) scales (Maier, Buller, Philipp, & Heuser, 1988), respectively. The sample characterization is presented on Table 1.

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Hospital de Braga (Portugal). The study goals were explained, and written informed consent was obtained from each participant.

Gambling task

During the fMRI session, participants performed a card gambling task, adapted from Macoveanu and colleagues (2013). The experimental task was implemented in two separate runs. In each trial, participants were informed about the accumulated reward and of the value of the upcoming bet. Afterwards, participants were presented with a screen displaying seven cards face down, randomly distributed into two decks. The "ace of hearts" was hidden in one of these decks. Participants had to guess the deck containing this card to receive a reward; or, otherwise, lose the bet (Figure 1A). The task was comprised of distinct risk levels, with a parametric variation of the odds (range of probability: 1/7 to 6/7) (Figure 1B). The task was presented as an even distribution of choices across all risk levels, enabling us to study risk-seeking and risk-avoidance behavior. In this study, we focused on the analysis of the risk-taking behavior.

MRI acquisition

Imaging was performed using a clinical approved 1.5 T Siemens Magnetom Avanto MRI Scanner (Siemens, Erlangen, Germany) using a 12-channel receive-only head coil. A structural T1-weighted 3D MPRAGE (magnetization prepared rapid gradient echo) scan was acquired, using the following parameters: 176 sagittal slices, repetition-time (TR) = 2730 ms, echo-time (TE) = 3.48 ms, slice thickness = 1 mm, slice gap = 0 mm, voxel size = 1x1x1 mm^2, field-of-view (FoV) = 256×256 mm, flip angle (FA) = 7°. For the functional MRI scan, a t2*-weighted Echo Planar Imaging (EPI) sequence, sensible to a blood oxygen level-dependent (BOLD) contrast was acquired in two consecutive runs (each with 315 volumes) with a minute break in-between. The

EPI sequence had the following characteristics: number of slices = 38, TR = 2500 ms, TE = 30 ms, slice thickness = 3 mm, voxel size = 3x3x3.6 mm, FoV = 256×256 mm, FA = 90°.

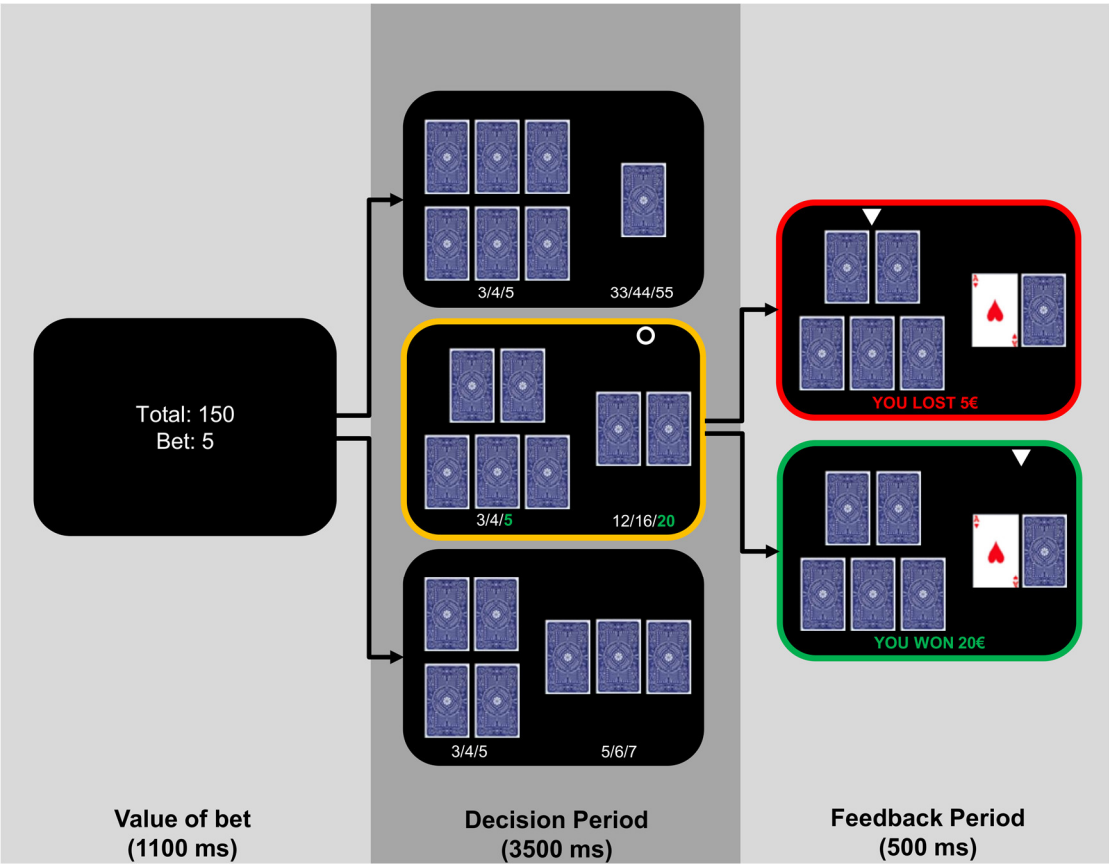

Figure 1. The gambling task. At the beginning of each trial (Information phase), participants were informed about the amount of accumulated money and the value of the current bet; next (Decision phase), two decks were displayed facedown; finally (Outcome phase), the location of the ace of arts was displayed and the subjects received the feedback indicating that they either won or lost the bet.

MRI processing

The preprocessing pipeline of the functional scans was implemented using SPM12 and included the following steps: (1) slice-timing correction, (2) realignment of the acquired functional images to the mean to correct for head motion, (3) co-registration of the T1-MPRAGE structural image to the mean EPI, (4) normalization of subjects' images into MNI space, (5) spatial

smoothing with an 8-mm full-with al half maximum (FWHM) kernel. All the resulting images were subjected to visual inspection for quality control.

Statistical analysis

The analysis of the number of responses and reaction time for different risk levels was conducted using Mixed-Design Factorial ANOVA models, where the group was defined as between-subjects' factor and risk-level as within-subjects' factor. Since the experimental paradigm was a forced-choice design with paired risk levels, only three conditions were considered (1/7 with 6/7, 2/7 with 5/ and 3/7 with 4/7) for the number of choices, with the goal of avoiding collinearity. For the analysis of reaction times, each of the six risk levels was considered individually.

First-level analysis was conducted by modelling three regressors for the choice phase (high, medium and low risk-levels) and six regressors for the outcome phase (negative and positive outcomes for high, medium and low risk-levels). Six nuisance regressors - corresponding to three directions of translation and three axes of rotation – were also included in the model. Regressors were convolved with the canonical hemodynamic response function (HRF).

For the second level analysis, voxel-wise analyses were implemented using GLM Flex (http://mrtools.mgh.harvard.edu/index.php/Main_Page) using Mixed Design ANOVA models, with one within-subjects' factor (risk level) and one between-subjects' factor (group). The contrasts resulting from the first-level analysis were included for the estimation of within- and between-group effects. Two distinct approaches were implemented to detect statistically significant differences: (1) a fully exploratory model, in which no theoretical regions of interest (ROIs) were defined; (2) a ROI-derived approach. For the first approach, 10.000 Monte Carlo simulations were implemented using 3dFWHMx (estimating intrinsic smoothness based on residuals) and 3dClustSim (estimating probability of false positives) packages (together with the autocorrelation function; -acf) from the AFNI software package (Ward, 2000; updated April 2016), which enables an accurate estimation of cluster size, controlling familywise error and accounting for spherical non-Gaussian spatial autocorrelation of the fMRI signal. Results from these simulations indicated that, considering voxel-wise intensity thresholds of $p < .001$ and

p<.005 (restricted to the group-level brain mask), cluster extent thresholds of 110 and 250 contiguous voxels (for the first and second, intensity thresholds, respectively) would be necessary to achieve an overall Type I error rate of $p < .05$, corrected for multiple comparisons.

For the second approach, and following the strategy implemented in previous reports, ROI analyses were also conducted on regions consistently implicated in the processing of expected value and reward, including striatal nuclei (including the caudate, putamen and the nucleus accumbens), insula, OFC and ACC and amygdala as reported in a meta-analysis of neuroimaging studies (Liu, Hairston, Schrier, & Fan, 2011). All ROIs were anatomically defined based on the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). For the ROI-based approach, a mask including the abovementioned ROIs was created. An arbitrary uncorrected p-value of p<.005 with a minimum cluster extension of 10 contiguous voxels was considered for the determination of statistical significance. This approach has been previously used to deal with the small size of a priori structures, such as the nucleus accumbens (Giuliani & Pfeifer, 2015; Guassi Moreira & Telzer, 2018; Van Hoorn, McCormick, Rogers, Ivory, & Telzer, 2018). Post-hoc analyses were performed to compare the BOLD signal between risk conditions and for the decomposition of interaction effects.

The mean BOLD signal for each (whole-brain and ROI level) result was extracted for posterior analysis. Correlation analyses were implemented to assess the impact of clinical features (Y-BOCS, HAM-A and HAM-D total scores) on behavioral and/or neuroimaging findings. We relied on the combined use of frequentist and Bayesian analyses. The latter approach has been used to handle with the multiple comparisons. For the Bayesian analysis, two models are compared for each pairwise association: the null hypothesis model (H0), which assumes a bivariate normal distribution with zero covariance and the alternative hypothesis model (H1) which assumes that variables are distributed according to a bivariate normal distribution with a non-zero covariance are related (Quintana & Williams, 2018). Bayes factors (BF) – the ratios between the marginal likelihoods of the alternative and null models – were interpreted according to Jeffreys' (Jeffreys, 1998) cutoffs: anecdotal (BF_{10} between 1 and 3), moderate (BF_{10} between 3 and 10), strong (BF_{10} between 10 and 30), very strong (BF_{10} between 30 and 100) or extreme (BF_{10}>100) relative evidence. The association between clinical variables and fMRI results were implemented in JASP (version 0.9.0).

Results

Behavioral results

OCD patients and healthy controls display similar proportions of choices across the six risk levels. A linear distribution of choices was observed across descending risk levels, *i.e.,* participants made considerably more low-risk choices. In addition, there was a significant effect of risk level on the reaction times ($F_{(3.9, 224.7)}$=3.943, p<.001), which fit a quadratic function, such that the choice 2/7 and 3/7 were associated with longer response times.

Patterns of brain activity during the decision phase

There were significant effects of risk condition on patterns of brain activity, such that higher-risk elicited increased activation of the NAcc, anterior insula and ACC. On the other hand, it was noted that the activity of the posterior insula (ROI-approach) was significantly reduced in response to high-risk choices (Table 2; Figure 2).

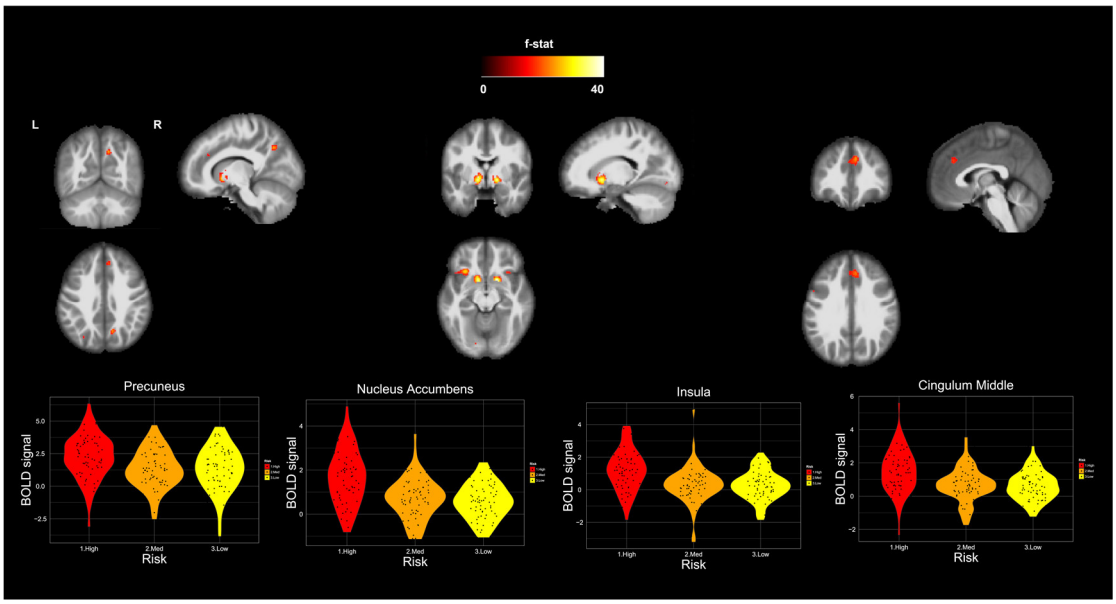

Figure 2. Main effects of condition on patterns of brain activity during the decision-phase. High-risk choices are associated with an increased brain activity of the precuneus, nucleus accumbens, anterior insula and cingulum middle. In contrast, low-risk choices are associated with an increased activity of the posterior insula.

Significant effects of group were observed during the choice phase on the activity of the posterior cingulum, lingual gyrus and ACC, with OCD patients displaying decreased activation of these regions during the decision phase, independently of the risk condition (Figure 3A). Group-by-risk interaction effects were using the ROI-approach, where significant group-by-risk interactions were found for the amygdala and ACC. Post-hoc analysis indicated that OCD patients displayed a larger reduction of the BOLD signal in this region during high-risk choices, in comparison to low-risk; the opposite pattern was observed for the HC group (*i.e.,* larger deactivation of the amygdala for low-risk options). On the other hand, it was noted that the HC group present a larger deactivation of the ACC during high-risk choices (comparing to low-risk choices), while the OCD group was characterized with a larger ACC deactivation during low-risk (Figure 3B).

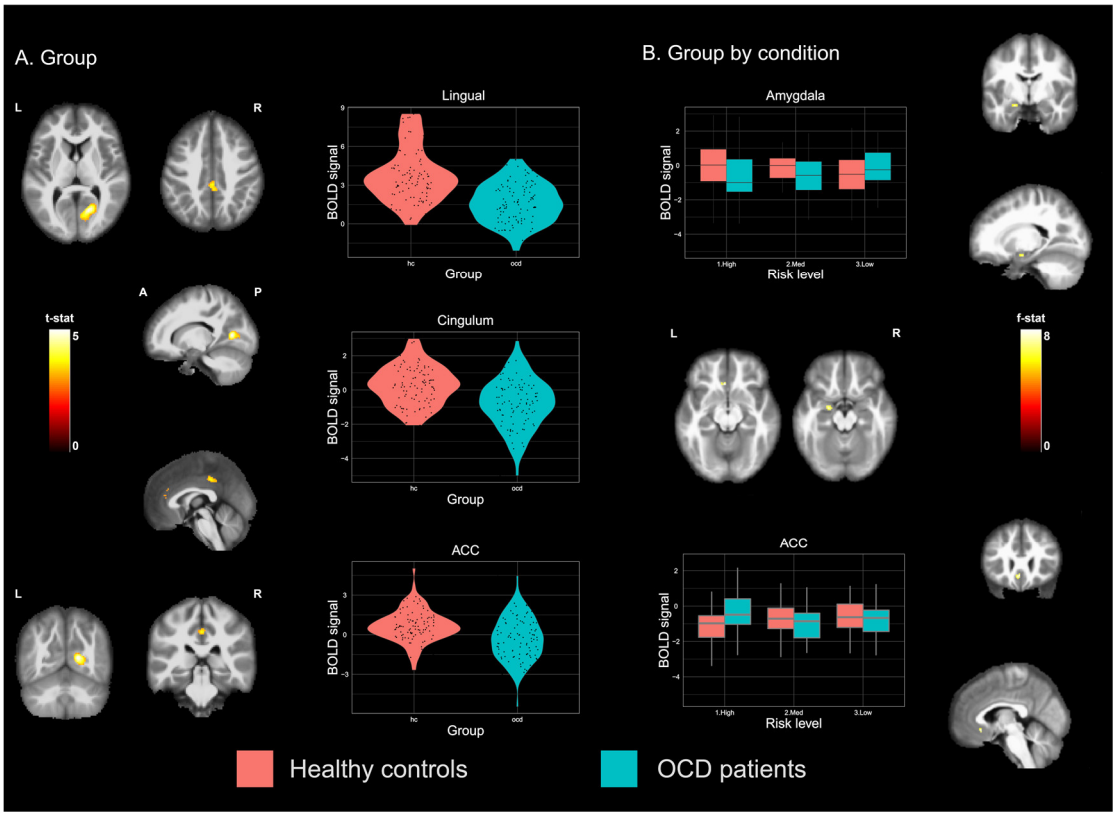

Figure 3. (A) Effects of group during the decision phase. Group has a significant effect on the patterns of brain activity of the (1) posterior cingulum, (2) lingual gyrus and (3) ACC. (B) Group by Condition effects during the decision phase on the amygdala and ACC.

Brain response during the outcome phase

In the outcome phase, it was observed that while there were no main effects of group on patterns of brain activity, there were significant effects of condition, with both groups showing

a larger activation of the cerebellum and anterior insula in response to negative outcomes with higher-risk levels. Furthermore, significant (ROI approach) group by condition interaction effects were found in the ACC and left Putamen. The OCD group revealed considerably greater deactivation of these regions in response to negative outcomes of low-risk choices; on the other hand, the HC group had larger deactivations to negative outcomes of high-risk choices (Table 3; Figure 4). No significant (main or interaction) effects were observed for positive outcomes.

Association between brain activity and clinical measures

For the group of OCD patients, there was moderate evidence (BF_{10}=9.37) for the association between the BOLD signal of the lingual gyrus to high-risk choices (*i.e.,* 1/7 and 2/7 risk-levels) in the decision phase and the severity of the disorder (*i.e.,* total Y-BOCS score).

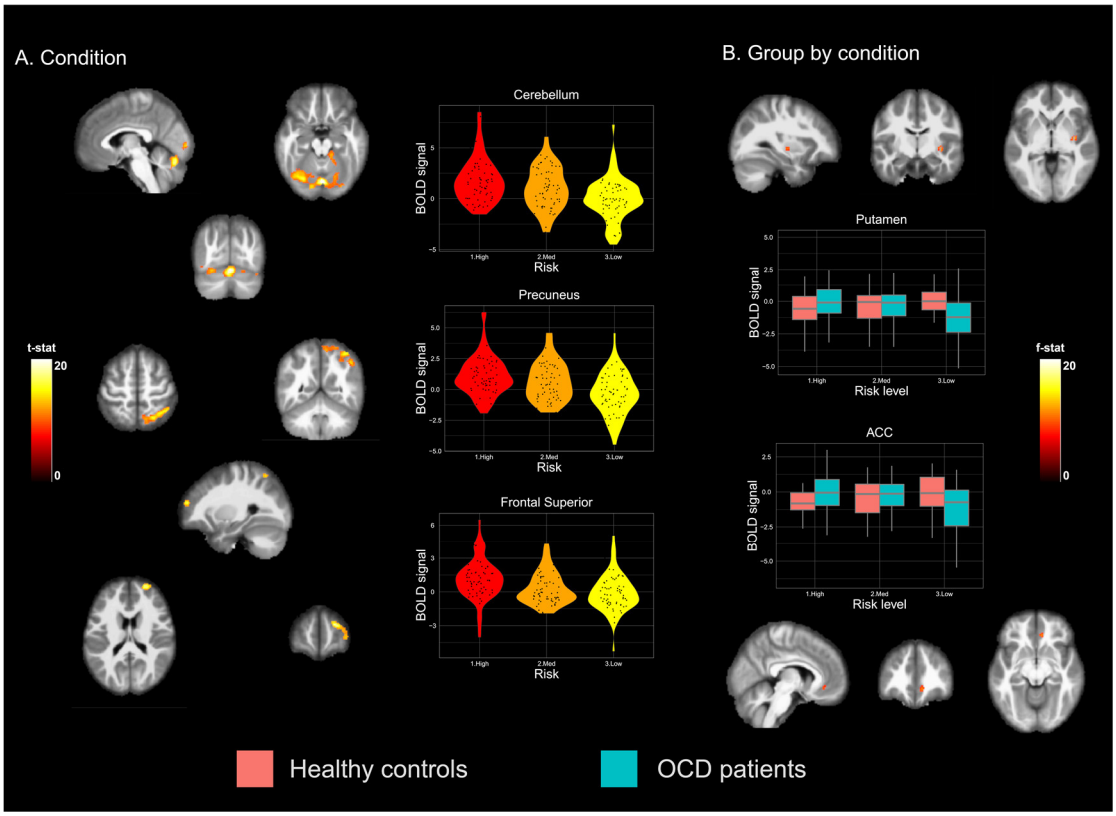

Figure 4. A. Condition effects during the feedback to losses. High-risk choices are characterized by a significantly increased activity of the cerebellum, precuneus and frontal superior. Significant group-by-risk interactions were observed for the ACC and Putamen. For these regions, there was a reduction of the BOLD signal for high-risk choices in the HC group; on the opposite, there was a reduction of the BOLD signal for low-risk choices in the OCD group.

In a similar fashion, there was a significant association between the activity of the posterior cingulum to high-risk choices and depression scores (r=.419, p=.030) – however, the interpretation of the Bayesian analysis provided only anecdotal evidence for these associations (BF_{10}=2.25). Similarly, significant (uncorrected) results, with anecdotal evidence for the alternative hypothesis (BF_{10}=1.68) were obtained for the association between the activity of the precuneus during the decision period to mid-risk choices (*i.e.,* 3/7 and 4/7 risk-levels) and anxiety scores (r=.393, p=.043). Lastly, there was a significant association, with anecdotal relative evidence (BF_{10}=1.57), between the activity of the putamen to low-risk level choices during the outcome phase and Y-BOCS total score (r=.356, p=.042). The full description of the results of the correlation analyses for the significant (whole-brain and ROI levels) brain activity findings is presented on Table 4.

Discussion

In this work, we conducted a functional MRI study to examine the neural correlates of risky decision-making in OCD patients. We observed that OCD patients are characterized by altered patterns of brain activity during decision and feedback phases on a gambling task, in comparison to healthy individuals. The most pronounced findings were associated with clinical characteristics of the disorder, namely the severity of obsessive symptoms and anxiety levels.

During the decision phase, there was a significant effect of decision risk, such that higher-risk choices were associated with an increased activation of the NAcc and anterior insula, in comparison to low-risk choices. It has been repeatedly advocated that the anterior insula is relevant for higher-level processing, being tightly synchronized with frontal brain regions implicated in executive functioning (Eckert et al., 2009). In addition, an increased activation of the anterior insula has been associated with the risk level in previous studies (Macoveanu, Miskowiak, Kessing, Vinberg, & Siebner, 2016), which may suggest an involvement of the anterior insula in learning the negative value of loss-prediction cues (Morgado et al., 2015; Palminteri et al., 2012). Neuroimaging evidence has implicated the ventral striatum on risky decision-making processing. Namely, its activity was previously associated with value encoding

(Christopoulos, Tobler, Bossaerts, Dolan, & Schultz, 2009) and hypothesized to be an important brain hub for the representation of loss aversion (Tom, Fox, Trepel, & Poldrack, 2007).

On the opposite, the activation of the posterior insula was associated with lower-risk levels. Altogether, these results demonstrate the importance of these brain regions in the context of risky decision-making, but also that different divisions of the insula play opposing roles during risk processing. Meta-analytic evidence highlights distinct functional connectivity profiles for different divisions of the insula: whereas the anterior division links mainly to emotion-related (*e.g.,* amygdala, ventral tegmental area and lateral OFC) and cognition-related (*e.g.,* ACC and dorsolateral prefrontal cortex), the posterior insula is selectively connected to sensorimotor areas (Chang, Yarkoni, Khaw, & Sanfey, 2012). Our results can also be interpreted in the context of the role of differential involvement of insular divisions on risk processing. A recent review proposed that the anterior insula plays a critical role on tracking arousal, magnitude and risk prediction error; on the other hand, the posterior insula is mainly involved on urge processing and signaling homeostatic imbalance during the evaluation of risky gambles (Droutman, Bechara, & Read, 2015).

Still regarding the decision phase, OCD patients displayed a significantly reduced activation of the posterior and anterior cingulate areas, independently of the risk-level. The ACC is of upmost relevance for the integration of risk and payoff and therefore, for learning the value of actions (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006). The activity of different divisions of the ACC has been linked to several behavioral impairments in OCD patients, such as error-processing abnormalities (Fitzgerald et al., 2005). On the other hand, the posterior cingulum is one important cluster of the default-mode network, which has been extensively described has a network of brain regions implicated in emotion processing and self-referential activity, including introspection (Liemburg et al., 2012). The involvement of visual areas on the pathophysiology of psychiatric disorders has been receiving accumulating evidence during recent years. Altered functional connectivity between the lingual gyrus and the insular cortex has been reported for the autism spectrum disorder (Odriozola et al., 2015) and addiction (Addicott, Sweitzer, Froeliger, Rose, & McClernon, 2015). Furthermore, in addition, recent neuroimaging studies reported reduced occipital activation in bipolar patients during periods of mania or depression, but not during euthymic states (Shaffer et al., 2017). In accordance with this notion, the lingual gyrus – the occipital division we found to be hyper activated in the OCD group (which

was also associated with the severity of the disorder) – has been implicated in the processing of emotionally charged content (Mitterschiffthaler et al., 2003) and in the generation of somatic arousal (Critchley, Elliott, Mathias, & Dolan, 2000). We have previously identified the lingual gyrus as a critical node of a network with diminished functional connectivity in OCD patients (Moreira et al., 2017).

OCD patients display a substantially larger reduction of the BOLD signal in the amygdala in response to high-risk choices in comparison to healthy individuals, during the decision phase. This suppression seems to be in accordance with the view that OCD patients are characterized by an altered emotional processing, marked by a decreased emotional regulation ability (Fergus & Bardeen, 2014) and a negative bias towards emotional stimuli, such that these stimuli are viewed as more unpleasant and less controllable (Casado, Cobos, Godoy, Machado-Pinheiro, & Vila, 2011). In fact, a recent meta-analytic investigation revealed that OCD patients are characterized by altered brain response of the amygdala during emotional processing (Thorsen et al., 2018). Previous studies highlighted that the synchrony between the amygdala and frontal brain areas underlines a limbic interference during cognitive processing in OCD individuals (de Vries et al., 2014). According to this, it seems reasonable to suggest a limbic interaction with other brain areas during risky decision-making behavior. Future studies may address this hypothesis, by assessing the patterns of covariance between limbic regions and higher-order processing-related areas, such as the ACC and the OFC, during risky decision-making.

During the feedback to losses, both groups were characterized by significantly cerebellar BOLD increases in response to losses. To the best of our knowledge, the involvement of the cerebellum in the processing of losses during decision-making tasks is still under-explored. Previous lesion studies have demonstrated that cerebellar damage contribute to altered decision-making behavior (Clausi et al., 2015; de Oliveira Cardoso et al., 2014).

Lastly, there were significant group-by-risk interactions in the ACC and Putamen. For all these regions, OCD patients displayed a larger reduction of the BOLD signal during the feedback to low-risk vs high-risk choices, whereas healthy individuals display a larger reduction for high-risk choices. In other words, OCD patients displayed suppression of the activity of these brain regions when they perceived unexpected losses. This set of brain regions has been repeatedly involved in goal-directed decision-making, particularly in learning the sequences of stimuli that leads to the reward (Hollerman, Tremblay, & Schultz, 2000). In the case of OCD, a recent report

described that OCD patients are characterized by abnormal reward prediction errors' signaling in the ACC and putamen, which may conduct to an increased indecisiveness and intolerance to uncertainty (Hauser et al., 2017). Thus, it seems reasonable to suggest that abnormal functioning of these hubs during risky decision-making OCD constitute a brain response to the processing of unexpected losses.

Some considerations may be raised for this work. Due to the high heterogeneity of behavioral manifestations of the disorder across different subtypes, it would be interesting to investigate between-subtype differences. Indeed, previous findings have suggested that specific subtypes of the disorder may be particularly susceptible to behavioral performance during decision-making tasks (Lawrence et al., 2006). Nevertheless, grouping OCD patients by subtype would limit the statistical power of our analysis. Another important question concerns the characteristics of the risky decision-making task used here. Whereas this task is highly advantageous for discriminating between opposing levels of risky decision-making, its nature forces the participants to select between two risk alternatives. This limits the discrimination between participants for each decision-making scenario and may possibly impact between-group differences. Future studies may address risky decision-making characteristics in OCD patients, by allowing the participant to select between multiple risk choices

In sum, these findings highlight that OCD is characterized by abnormal patterns of brain function during "hot" processing of decision-making. This may provide new insights regarding the relevance of affective processes for decision-making ability in these patients. As such, future studies may address the interaction between decision-making and affective processing and extend the characterization of decision-making to other under-explored domains, where the affective component of the decisions has more salience, such as the characterization of OCD patients in social-decision making scenarios.

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Disclosures

The authors have no conflict of interest to disclose. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The paper has not been published previously, or is under consideration for publication elsewhere, in English or in any other language.

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Table 1. Socio-demographic and clinical characteristics of patients with obsessive-compulsive disorder and healthy comparison subjects

Characteristic	OCD (n=34)	HC (n=33)	Difference
Age, Years	25.76 ± 6.66	25.63 ± 5.43	ns
Education, Years	13.48 ± 2.20	14.63 ± 3.20	ns
Sex, n (%) Males	16 (47.1%)	15 (45.5%)	ns
Y-BOCS, Total Score	25.24 ± 7.14	–	–
Y-BOCS, Obsessions	13.79 ± 4.11	–	–
Y-BOCS, Compulsions	11.45 ± 3.59	–	–
HAM-A-, Total Score	6.26 ± 7.13	–	–
HAM-D-, Total Score	5.52 ± 4.31	–	–

Values are presented as mean ± SD.
Y-BOCS, Yale-Brown Obsessive Compulsive;
HAM-A, Hamilton Anxiety Rating Scale; HAM-D, Hamilton Depression Rating Scale.

Table 2. Effects of condition during the anticipation phase

	p<.05 (FWE-corrected)					p<.005				
	k	Peak Int	x	y	z	k	Peak Int	x	y	z
Effect of risk										
	161	43.34	16	10	-6					
	253	40.95	-12	8	-6					
	186	30.4	-30	22	-8					
	44	26.49	12	-64	40					
	211	25.89	6	36	34					
	23	22.37	32	20	-6					
	33	21.01	-48	-44	56					
	11	16.19	-12	-86	-10					
						86	9.03[a]	42	-10	4

[a]Uncorrected results for ROI-driven approach; Peak Int – Peak intensity for each displayed result; k – cluster extension; Coordinates are presented in the MNI standard space

Table 3. Effects of group and condition by group interactions during the anticipation phase

	p<.001					p<.005				
	k	Peak Int	x	y	z	k	Peak Int	x	y	z
OCD<Control										
	427	5.33	20	-64	8	1240	5.33	20	-64	8
						278	3.86	0	-32	42
						159	3.6[a]	-4	32	28
Group by condition										
						18	7.66[a]	-22	-6	-18
						12	8.34[a]	-4	26	-12

[a]Uncorrected results for ROI-driven approach; Peak Int – Peak intensity for each displayed result; k – cluster extension; Coordinates are presented in the MNI standard space

Table 4. Effects of condition, group and condition*group during the feedback to losses

	p<.05 (FWE-corrected)					p<.005				
	k	Peak Int	x	y	z	k	Peak Int	x	y	z
Effect of risk										
	54	21.2	2	-78	-20					
	14	19.12	22	58	20					
Group by condition										
						46	11.21[a]	36	-12	-2
						46	9.32[a]	8	36	-10

Table 5. Association between significant brain findings and clinical measures

		Decision Period									Loss				
Risk Level	**Scale**	**Nacc_C**	**Ins_C**	**Cing_C**	**Prec_C**	**Lingual_G**	**Cing_G**	**ACC_G**	**Amyg_I**	**ACC_I**	**Cer_C**	**Prec_C**	**FSup_C**	**Putamen_I**	**ACC_I**
High	HAS	r=0.072, BF10=0.254	r=-0.166, BF10=0.331	r=0.309, BF10=0.768	r=0.332, BF10=0.928	r=-0.043, BF10=0.244	r=-0.013, BF10=0.239	r=-0.017, BF10=0.24	r=-0.042, BF10=0.244	r=-0.055, BF10=0.248	r=-0.163, BF10=0.327	r=-0.107, BF10=0.274	r=-0.066, BF10=0.251	r=-0.328, BF10=0.902	r=0.006, BF10=0.239
	HDS	r=0.009, BF10=0.239	r=-0.07, BF10=0.253	r=0.419*, BF10=2.252	r=0.057, BF10=0.248	r=-0.077, BF10=0.256	r=-0.234, BF10=0.462	r=0.119, BF10=0.283	r=-0.123, BF10=0.286	r=0.193, BF10=0.371	r=-0.133, BF10=0.294	r=-0.251, BF10=0.509	r=0.126, BF10=0.288	r=-0.247, BF10=0.499	r=0.15, BF10=0.311
	YBOCS	r=0.082, BF10=0.239	r=0.063, BF10=0.229	r=0.307, BF10=0.924	r=0.116, BF10=0.264	r=0.477*, BF10=9.37	r=-0.081, BF10=0.238	r=0.096, BF10=0.248	r=0.175, BF10=0.341	r=0.143, BF10=0.293	r=0.193, BF10=0.378	r=0.226, BF10=0.466	r=0.136, BF10=0.284	r=0.02, BF10=0.218	r=0.039, BF10=0.222
Mid	HAS	r=0.108, BF10=0.274	r=0.024, BF10=0.241	r=0.192, BF10=0.37	r=0.393*, BF10=1.684	r=-0.094, BF10=0.265	r=0.202, BF10=0.388	r=0.266, BF10=0.561	r=-0.111, BF10=0.276	r=0.054, BF10=0.247	r=-0.049, BF10=0.246	r=-0.032, BF10=0.242	r=0.038, BF10=0.243	r=0.001, BF10=0.239	r=0.281, BF10=0.622
	HDS	r=0.105, BF10=0.272	r=0.207, BF10=0.399	r=0.365, BF10=1.263	r=0.127, BF10=0.289	r=-0.053, BF10=0.247	r=0.13, BF10=0.291	r=0.308, BF10=0.761	r=0.002, BF10=0.239	r=0.071, BF10=0.253	r=-0.142, BF10=0.303	r=-0.059, BF10=0.249	r=0.275, BF10=0.599	r=0.116, BF10=0.28	r=0.262, BF10=0.548
	YBOCS	r=0.151, BF10=0.303	r=0.238, BF10=0.506	r=0.282, BF10=0.729	r=0.091, BF10=0.244	r=0.306, BF10=0.913	r=0.011, BF10=0.217	r=0.307, BF10=0.925	r=0.277, BF10=0.697	r=0.096, BF10=0.248	r=0.001, BF10=0.217	r=0.018, BF10=0.218	r=0.217, BF10=0.439	r=0.215, BF10=0.431	r=0.113, BF10=0.261
Low	HAS	r=0.075, BF10=0.255	r=0.067, BF10=0.252	r=0.26, BF10=0.54	r=0.276, BF10=0.6	r=-0.142, BF10=0.303	r=0.137, BF10=0.298	r=-0.033, BF10=0.242	r=-0.08, BF10=0.257	r=-0.167, BF10=0.332	r=0.042, BF10=0.244	r=0.111, BF10=0.276	r=0.129, BF10=0.29	r=-0.114, BF10=0.279	r=0.02, BF10=0.24
	HDS	r=0.111, BF10=0.276	r=0.246, BF10=0.493	r=0.362, BF10=1.23	r=0.109, BF10=0.275	r=-0.095, BF10=0.266	r=0.13, BF10=0.292	r=0.134, BF10=0.295	r=-0.011, BF10=0.239	r=0.007, BF10=0.239	r=0.235, BF10=0.463	r=0.092, BF10=0.264	r=0.234, BF10=0.46	r=0.018, BF10=0.24	r=0.196, BF10=0.377
	YBOCS	r=0.075, BF10=0.235	r=0.187, BF10=0.364	r=0.164, BF10=0.323	r=0.13, BF10=0.278	r=0.248, BF10=0.549	r=0.079, BF10=0.237	r=0.103, BF10=0.253	r=0.233, BF10=0.49	r=0.083, BF10=0.239	r=0.333, BF10=1.203	r=0.087, BF10=0.242	r=0.09, BF10=0.244	r=0.356*, BF10=1.566	r=0.287, BF10=0.763

CHAPTER 2.5

Functional connectivity of the neurobiological mechanisms underlying emotional processing in OCD: a meta-analytic investigation

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Functional connectivity of the neurobiological mechanisms underlying emotional processing in OCD: a meta-analytic investigation

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Abstract

In this work, we performed an aggregation of neuroimaging studies investigating the neurobiological mechanisms of emotional processing in obsessive-compulsive disorder (OCD), using an activation-likelihood estimation approach. Task-based and task-free functional connectivity analysis were performed with the aim of identifying areas of significant co-activation with the regions derived from a recent activation likelihood estimation analysis and of characterizing these regions with respect to their functional associations. A set of regions of interest, including Broadmann area 9, substantia nigra and right putamen were found to be consistently hyper-active in OCD patients in tasks involving emotional processing. These areas were functionally connected with the co-activation of emotional processing related regions with the cingulate cortex, insular regions and basal ganglia nuclei. These results suggest the relevance of the emotional processing in OCD patients for a set of other behavioral dimensions – particularly related with value-based decision-making. This raises the possibility that interventions tackling emotional processing may be important for improving other domains of the disorder, such as an over-reliance on habitual behaviors – which is highly associated with an impaired update of the reward system.

Background

Obsessive Compulsive Disorder (OCD) is one of the most debilitating psychiatric conditions. It has an extreme impact on several life domains, including occupational, academic and social functioning. The pathophysiology of the disorder has been characterized at behavioral, clinical and neurobiological levels. Behaviorally, OCD is associated with the occurrence of obsessive thoughts, which causes high levels of anxiety in these patients. Ritualistic acts are performed to reduce this anxiety. Even though abnormalities within cortico-striatal loops are advocated as central features of the pathophysiology of the disorder, these neurobiological mechanisms do not fully account for the some symptomatological expressions of these patients (Menzies et al., 2008). One such example pertains to the intense emotional responses associated with anxiety. Accumulating evidence has highlighted the relevance of other circuits, such as cortico-limbic pathways, as potential key players underlying these clinical manifestations (Admon et al., 2012; Picó-Pérez et al., 2018).

This perspective is supported by the results of recent functional magnetic resonance imaging (fMRI) findings, which reveal that OCD patients display an increased brain response of the amygdala, striatum and orbitofrontal cortex (OFC) during the anticipation of emotional stimuli. Altered functional connectivity (FC) of the amygdala with frontal and with the insula and posterior regions during emotional regulation has recently been highlighted (De Wit et al., 2015; Via et al., 2014). A recent meta-analytic aggregation of the literature of neuroimaging studies has demonstrated that OCD patients display consistent patterns of increased activation in several brain nodes, including amygdala, right putamen, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC) ventromedial prefrontal cortex (VMPFC), middle temporal cortex and left inferior occipital cortex (Thorsen et al., 2018b). Of note, OCD patients are also characterized by an altered pattern of brain activation during risky-decision making, involving amygdalar activations to threat, as well as reduced functional connectivity (FC) of the amygdala with frontal brain regions. Altogether, this combined literature provides support for the importance of other brain networks (not captured in the cortico-striatal-thalamic-cortical (CTSC) circuit) for the pathophysiology of the disorder. Furthermore, the fact that these patients display an altered brain response of the limbic system during risky decision-making raises the hypothesis that impaired emotional processing/regulation ability may underline an impaired decision-making processing.

The current work

In this work, we departed from a recently published meta-analytic aggregation regarding the neural correlates of emotional processing in OCD patients (Thorsen et al., 2018b). We re-conducted a meta-analytic aggregation of a subset of studies to obtain maps of a more homogeneous set of studies. The meta-analytic results were then analyzed with respect to their patterns of functional connectivity, using task-based and task-free analyses.

Methods

Activation Likelihood Estimation

The selection of studies was based on a recently published meta-analytic aggregation of neuroimaging studies investigating the neurobiological correlates of emotional processing in OCD patients (Thorsen et al., 2018a). With the goal of maximizing between-studies' homogeneity, we restricted our analysis to those studies using visual or auditory modalities for emotional induction. We excluded studies related to moral decision-making, using pediatric samples or imaging modalities other than fMRI experiments. According to these criteria, we considered a final list of thirteen studies, which are described on Table 1.

The aggregation of the final list of studies was implemented with the Activation Likelihood Estimation approach. Foci are represented as spatial probability distributions. This algorithm allows the computation of a coordinate-based meta-analysis by determining the convergence of foci reported from different individual studies. Considering that studies with larger sample sizes will be a more reliable approximation of the true estimates, these studies will be modelled with smaller Gaussian distributions. ALE scores were compared against an empirical null-distribution, corresponding to a random spatial association between groups. With the goal of controlling for false-positive rate, the statistical significance was defined considering a cluster-level family-wise error (FWE) correction at $p<.05$ and a cluster defining threshold of $p<.001$ and 1000 permutations.

Table 1. List of studies comparing the neural correlates of emotional processing in OCD patients with healthy controls

Study	Imaging modality	Task	N OCD	N HC	Mean age	% Males	Mean Y-BOCS	% Med
An et al. (2009)	fMRI	Symptom provocation using pictures	29	21	36.55	50.5	27.2	79.31
Banca et al. (2015)	fMRI	Symptom provocation using pictures	15	15	32	53.33	26	93.33
Basile et al. (2014)	fMRI	Emotional faces and guilt-inducing sentences	13	19	37	76.92	19.3	46.15
Berlin et al. (2015)	fMRI	Emotional Go/No-Go	9	10	38.33	55.5	23.35	42.11
Brennan et al. (2015)	fMRI	Emotional Stroop	30	29	32	60	27.8	80
Britton et al. (2010)	fMRI	Gender matching of emotional vs. neutral faces	12	17	13.8	58.33	17.8	100
Cannistraro and Rauch (2004)	fMRI	Emotional vs. neutral faces	10	10	26.8	40	26.3	0
Cardoner et al. (2011)	fMRI	Emotional face matching	21	21	28.5	47.62	20.7	95.2
deWit et al. (2015)	fMRI	Symptom provocation using pictures	43	38	38.4	49	21.6	0
Gonçalves et al. (2015)	fMRI	Symptom provocation using pictures	15	12	31.7	73.3	23.8	100
Han et al. (2016)	fMRI	Working memory task with emotional distractors	20	23	25.5	60	23.9	55
Harrison et al. (2012)	fMRI	Moral dilemmas	73	73	33.1	57.53	22.1	97.26
Hennig-Fast et al. (2015)	fMRI	Shame/guilt-related sentences	20	20	31.1	50	15.9	NR
Lawrence et al. (2007)	fMRI	Emotional vs. neutral faces	17	19	34.9	59	25.53	76.47
Mataix-Cols et al. (2004)	fMRI	Symptom provocation using pictures	16	17	35.8	50	24.7	75
Murayama et al. (2013)	fMRI	Symptom provocation using words	22	19	36.1	36.36	29.9	0
Park et al. (2016)	fMRI	Emotional working memory	16	16	31.4	75	25.3	NR
Phillips et al. (2000)	fMRI	Symptom provocation using pictures	14	14	34	50	28	78.57
Shapira et al. (2003)	fMRI	Symptom provocation using pictures	8	8	41.8	37.5	25.1	0
Thiel et al. (2014)	fMRI	Symptom provocation using pictures	15	15	43.3	50	24.9	0
van den Heuvel et al. (2004)	PET	Symptom provocation using pictures	11	10	40.5	72.72	23.8	0
van den Heuvel et al. (2005)	fMRI	Emotional Stroop	18	19	33.4	33.33	23.4	0
Via et al. (2014)	fMRI	Emotional face matching	67	67	33.1	56.72	21.8	97.01
Rus et al. (2017)	fMRI	Symptom provocation using pictures	42	37	32.5	35.71	17.7	62.3
Berlin et al. (2017)	fMRI	Olfactory symptom provocation	15	15	34.07	53.33	17.73	93.3

Abbreviations: HC, healthy controls; fMRI, functional magnetic resonance imaging; OCD, obsessive-compulsive disorder; PET, positron emission tomography; NR, not reported; Y-BOCS, Yale-Brown Obsessive-Compulsive Scale; % Med – percentage of patients receiving any type of pharmacological treatment. Included studies are highlighted in bold;

Task-based connectivity: Meta-analytic connectivity modeling

The accumulating extension of neuroimaging state of the art has been producing large volumes of data regarding the localization of neurobiological processes underlying different psychological, cognitive and sensorial aspects (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012). Nevertheless, neuroimaging experiments are typically accompanied by low reliability (Raemaekers et al., 2007) and low statistical power – which seems to be result from the combination a several amount of dependent variables, low sample sizes and a need to correct for multiple comparisons (Cremers, Wager, & Yarkoni, 2017).

Meta-analytic aggregation of neuroimaging research has been established as an important tool to identify consistent localizations across experiments (Eickhoff et al., 2009). These procedures allow researchers to compare results across studies in the absence of primary data (Laird et al., 2009; Poldrack et al., 2008). The use of meta-analytic strategies has more recently upgraded to accommodate to exploration of brain-wide functional connectivity patterns. This approach – termed meta-analytic connectivity modelling (MACM, Laird et al. (2013)) – examines which brain regions are co-activated above chance with a given seed region across a large and diverse set of neuroimaging experiments (Eickhoff et al., 2010; Robinson, Laird, Glahn, Lovallo, & Fox, 2010). With this strategy, MACM allows the distinction of spatial convergence from noise by comparing it against unbiased null-distributions of random spatial associations between experiments (Langner, Rottschy, Laird, Fox, & Eickhoff, 2014). MACM has been widely used to map the connectivity profile of specific brain regions, such as the cingulate cortex (Torta & Cauda, 2011), the caudate (Robinson et al., 2012), the orbitofrontal cortex (Zald et al., 2012), the amygdala (Robinson et al., 2010), the insula (Cauda et al., 2012), among others. In addition, MACM has also been used to functionally characterize the connectivity patterns formed by consistent structural or functional brain alterations in specific clinical and psychiatric conditions (*e.g.,* Dogan et al., 2015; Cortese et al., 2016).

MACM was implemented to establish connectivity patterns for increases for each ROI. The identification of co-activated areas was achieved with the BrainMap database (http://www.brainmap.org) (Laird, Lancaster, & Fox, 2005) – a large repository of peak coordinates as well as the associated meta-data reported in, approximately, 10.000 neuroimaging experiments. The locations reported for each ROI were exported in MNI space. For this study, the search was limited to activations on healthy subjects regardless of the behavioral

domain. The whole-brain coordinates were downloaded, and the areas of convergence were determined by analyzing the foci resulting from each ROI search.

Task-free connectivity: resting-state functional connectivity

Acquisition parameters

One resting-state fMRI (rs-fMRI) dataset was used to complement for the purpose of complementing task-based connectivity. Whole-brain resting-state FC was used to identify connectivity maps of the seeds resulting from the ALE aggregation. The functional images of 192 healthy individuals were obtained from Enhanced Nathan Kline Institute – Rockland Sample with a Siemens TimTrio 3T scanner. A total of 404 volumes were acquired with the following parameters: repetition-time (TR) = 1.4s, echo-time (TE) = 30 ms, flip-angle (FA) = 65°, voxel-size=2.0mm^3, 64 slices. During the rs-fMRI acquisition, participants were instructed to focus on a fixation cross, to try to think about anything in particular and to remain awake.

Pre-processing

Physiological and movement artifacts were removed from the functional images using FIX (FMRIB's ICA-based Xnoiseifier, version 1.061 as implemented in FSL 5.0.9; (Griffanti et al., 2014; Satterthwaite et al., 2013)). With this approach, the unique variance associated with artefactual components is regressed from the data together with 24 movement parameters (including derivatives and 2nd order effects as previously described and evaluated; cf. Satterthwaite et al., 2013). Data were further preprocessed using SPM8 (Wellcome Trust Centre for Neuroimaging, London) and in-house Matlab scripts. The first four scans were excluded prior to further analyses, the remaining EPI images corrected for head movement using a two-pass (alignment to the initial volume followed by alignment to the mean after the first pass) affine registration. Each subject's functional image was spatially normalized to the ICBM-152 reference space using the "unified segmentation" approach (Ashburner & Friston, 2005). The resulting deformation was applied to the individual EPI volumes, which were subsequently smoothed with

a 5-mm FWHM Gaussian kernel to improve the signal-to-noise ratio and to compensate for residual anatomic variations.

Results

ALE

The hyperactivated brain regions during emotional processing in the group of OCD patients, in comparison to healthy controls, are displayed on Table 2 and Fig. 1. Across the thirteen studies included in the meta-analytic aggregation, there was a convergent increased activity in the group of OCD patients in three clusters, with peaks on BA9, putamen and substantia nigra.

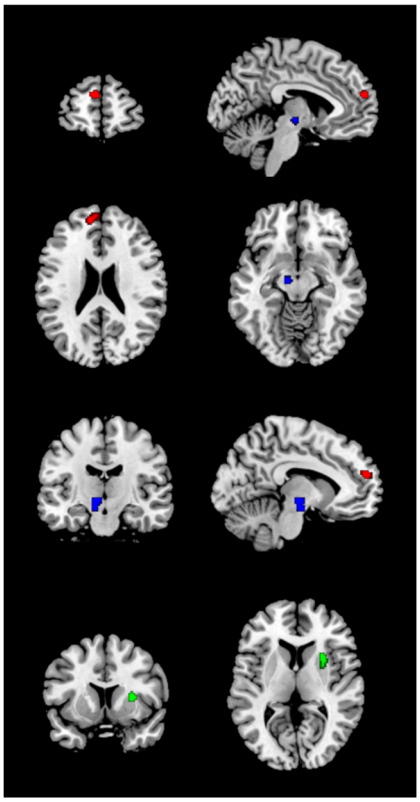

Figure 1. Results from the Activation Likelihood Estimation. Three significant clusters were obtained: a cluster located in Broadman Area 9 (in red), a cluster with the peak centered in substantia nigra (in blue) and a cluster with a peak in the right putamen (in green).

Table 2. Results from the activation-likelihood estimation (ALE) analysis

Cluster #	Volume (mm^3)	Extrema Value	x	y	z	Hemisphere	Region
1	800	0.019	-10	-14	-6	L	Subthalamic Nucleus
		0.018	-10	-12	-14	L	Substantia nigra
2	656	0.019	-6	58	20	L	Broadmann area 9
		0.017	-10	54	22	L	Broadmann area 9
3	592	0.018	28	10	10	R	Putamen

MACM

The patterns of functional co-activation are reported on Figure 2. For the seed located in BA9, the MACM revealed functionally connectivity with the prefrontal cortex and posterior cingulum (Figure 2A, Table 2). The seed located in the substantia nigra displayed higher connectivity with bilateral anterior insula, bilateral putamen, bilateral thalami (Figure 2B, Table 2). The seed located in the putamen had higher connectivity with the caudate, anterior insula, temporal regions and the cerebellum (Figure 2C, Table 2).

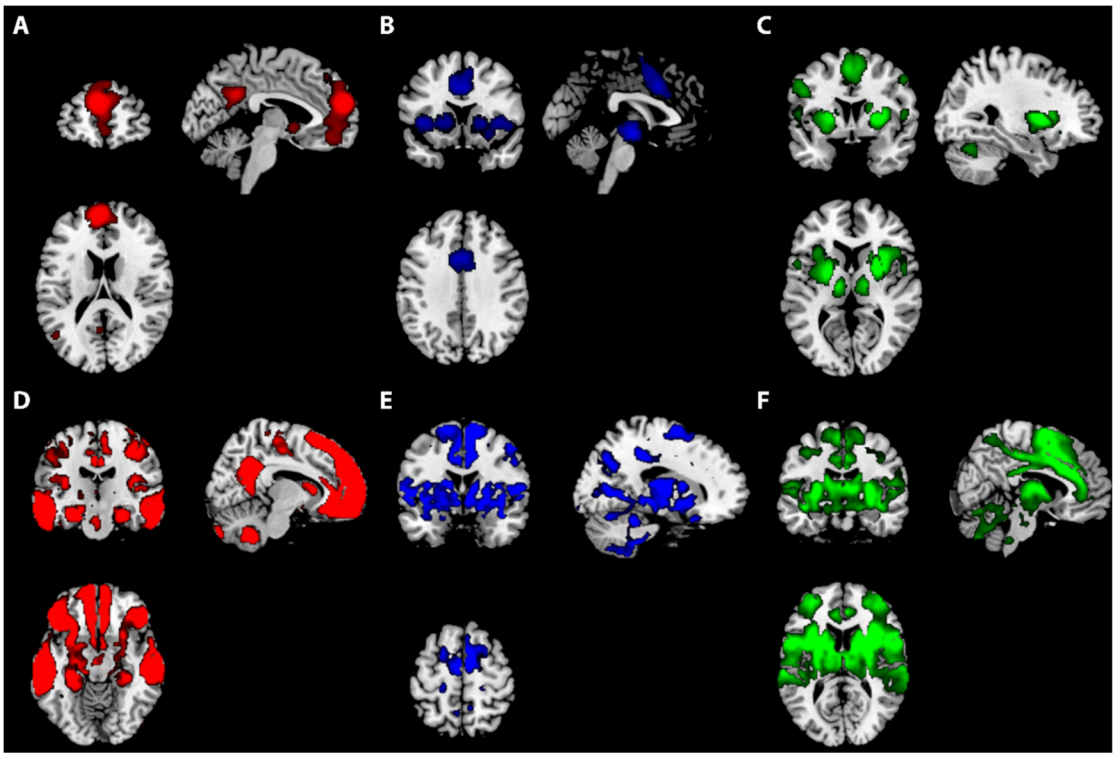

Figure 2. Meta-analytic connectivity modelling (top) and rs-fMRI FC (bottom) results. Resulting maps of task-based connectivity of (A) BA9, (B) Substantia nigra, (C) Right Putamen and of task-free connectivity of (D) BA9, (E) Substantia nigra, (F) Right Putamen.

Task-based functional connectivity

The analysis of rs-fMRI demonstrated that the seed located on BA9 (Fig. 2D) had statistically significant FC with a large portion of the frontal pole, including the medial prefrontal cortex (PFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC). In addition, this seed was functionally connected to temporal regions, insula, amygdala, posterior cingulum and cerebellum. The seed located on subtantia nigra had patterns of connectivity with dorsal and ventral divisions of the striatum, primary motor cortex, insula and cerebellum (Fig. 2E). Lastly, the seed on the right putamen displayed a connectivity profile with the dorsolateral prefrontal cortex (DLPFC) anterior, middle and posterior divisions of the cingulum, dorsal and ventral striatum, supplementary motor area, temporal regions (Fig. 2F).

Discussion

In this work, we implemented an activation-likelihood estimation analysis of neuroimaging studies to examine the neurobiological mechanisms of emotional processing in OCD patients. We re-conducted a meta-analytic aggregation of the emotional processing in OCD patients as reported in a previous publication, by selecting a more homogeneous set of studies. For this purpose, we focused only in studies with adult samples, reporting the results of whole-brain fMRI findings. We observed that there were consistent patterns of increased activation in three clusters with peaks on BA9, substantia nigra and right putamen. Task-based and task-free connectivity maps were obtained for each of these seed regions and functionally characterize the pattern of association of these seeds across the BrainMap database.

A common finding pertains to the connectivity of the resulting ALE seeds with striatal and insular brain regions. Besides being associated with topics such as emotion, autonomic function or higher cognitive tasks (Chang, Yarkoni, Khaw, & Sanfey, 2012), consistent patterns of insular activation have been reported in decision-making paradigms, including norm

compliance and fairness processing (Bellucci, Feng, Camilleri, Eickhoff, & Krueger, 2018). Specially for the substantia nigra and the putamen seeds, their pattern of connectivity also comprises the salience network, namely the bilateral insula and the dACC. The core function of the salience network is to mark salient events for additional processing and initiate appropriate control signals (Menon & Uddin, 2010), a function with critical importance for processes related to both emotional processing and decision making.

The findings of consistent activation partially overlap with the previous abovementioned publication. Nevertheless, the findings from Thorsen and colleagues (2018) include additional brain regions, such as bilateral amygdalae, ventral ACC and the occipital lobe. Some methodological considerations may help to explain these differences: first, we decided to restrict the pool of studies to a more homogeneous set, excluding experiments using tasks involving tasks such as moral decision-making, using pediatric samples and non-fMRI studies; the second aspect pertains to the method of aggregation of studies, which relied on Activation-Likelihood estimation, as opposed to the approach used in Thorsen's publication, which relied on effect-sized signal differential mapping (ES-SDM) (Radua et al., 2012). The chosen criteria will have an impact on the level of heterogeneity in a sample of experiments (Müller et al., 2018). Whereas it is true that the inclusion of more studies contributes to increased statistical power and to avoid that meta-analytic findings are driven by few experiments (Eickhoff et al., 2016), meta-analytic aggregations of neuroimaging studies face a tradeoff between the number of studies and the homogeneity between the included studies (Müller et al., 2017).

Finally, this meta-analytic aggregation focused exclusively on whole-brain analysis of neuroimaging data – as it is generally recommended for CBMA studies. This strategy accounts for the fact that the convergence across experiments is tested against a null-hypothesis of random spatial associations across the whole-brain, *i.e.,* each voxel has the same chance of being activated (Eickhoff et al., 2012). However, the exclusion of studies focused on a single region-of-interest may also raise additional bias, by excluding a considerable amount of studies (Müller et al., 2018). Possible solutions to handle this issue include the implementation of meta-analytic aggregations focused on a single ROI, in which the assumption of random distribution is delimited to that same ROI (Müller et al., 2018).

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Chapter 3. Psychophysiological correlates of emotional processing

CHAPTER 3.1

Emotional processing and the autonomic nervous system: a comprehensive meta-analytic investigation

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Emotional processing and the autonomic nervous system: a comprehensive meta-analytic investigation

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Abstract

The search for autonomic correlates of emotional processing has been a matter of interest to identify the physiological basis of emotion. Despite an extensive state-of-the-art exploring the correlates of emotion, there is no absolute consensus regarding how the body processes an affective state. In this work, we aimed to aggregate the literature of psychophysiological studies in the context of emotional induction. Two-hundred and ninety-one studies met the inclusion criteria and were quantitatively pooled in random-effects meta-analytic modelling. There was a negligible differentiation between emotional categories. Considerable amount of between-studies' heterogeneity was found in the meta-analytic aggregation. Self-reported ratings of emotional arousal were found to be associated with specific psychophysiological indices, particularly with the variation of the skin conductance level. Despite this clear association, there is still a considerable amount of unexplained variability that raises the need for more fine-grained analysis to be implemented in future research in this field.

1. Background

Current conceptualizations of emotion have been consistently influenced by William James' description of "what is an emotion?" in the 19th century (James, 1884). However, this has been a matter of relevance since the historical periods of ancient Greece and Rome, where emotion was widely perceived as a threat to reason and to philosophical thinking (Solomon, 1993). Despite the longstanding interest on the study of emotion and the accumulating state-of-the-art tackling this topic, a lot is still left to unravel. A matter of discussion pertains to the exact nature of the physiological correlates of emotional processing, as well as the exact role of bodily changes in emotion. Even though it is widely established that there are rich reciprocal connections between states in the central and peripheral nervous systems and what can be broadly described as emotional events, the direction of this association (*i.e.,* the cause-effect) is a matter of discordance (Larsen, Berntson, Poehlmann, Ito, & Cacioppo, 2008). One hypothesis – the Cannon-Bard theory (Cannon, 1927) – states that the efferent connections from the brain to periphery causes the peripheral variations in response to the subjective processing of emotions (*i.e.,* feelings). An opposite argument suggests that bodily changes follow directly the sensorial perception, which will not only precede, but will also generate the emotional experience (James, 1884). The third argument – the two-factor theory of emotion (Schachter & Singer, 1962) – shares a similar periphery-to-brain perspective, but suggesting that there is an undifferentiated peripheric response to different emotional states. Instead, the emotional experience will be cognitively interpreted, by conscientiously linking the experienced arousal with the situational context.

Psychophysiological correlates of emotional processing

The relevance of studying the brain/body correlates of emotional processing originally arises from the James-Lange theory of emotions, which highlights the close link between emotions and behavior. "Without the bodily states following on the perception, the latter would be purely cognitive in form, pale, colorless, destitute of emotional warmth. We might then see the bear, and judge it best to run, receive the insult and deem it right to strike, but we could not actually feel afraid or angry." (James, 1884). An extensive body of literature has examined the biological underpinnings underlying emotional processing, through the lens of central (central

nervous system level; CNS) or peripheral measurement (autonomic nervous system level; ANS). Altogether, these findings provide evidence for a reciprocal relationship between the bodily expression of emotion and how emotional information is attended. This underlines the central tenets in the theories of embodied cognition – the perspective that the perception and conceptualization of emotion involves perceptual, somato-visceral and motoric reexperiencing of the relevant emotion in one's self (Niedenthal, 2007).

The results from the meta-analytic aggregation of CNS measures are not consensual regarding the nature of the emotional processing on the brain: one branch of research suggests that different emotional categories have distinct signatures on brain correlates – supporting the view of the classical basic theories of emotion (Lench, Flores, & Bench, 2011); contrasting evidence points to non-specific patterns of brain response to the processing of discrete emotional categories (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012).

Many studies have characterized ANS responses to emotional processing by measuring the two main branches of this system: the sympathetic (which primes the body for action by, for instance, increasing the heart-rate) and the parasympathetic divisions (which aids in restorative functions; *e.g.,* simulation digestion). In general, ANS measures can be grouped according to different systems: electrodermal, cardiovascular, respiratory and facial (Table 1). Previous meta-analytic aggregations of the ANS correlates of emotional processing provided little evidence for different emotional categories, however with no evidence for discrete emotions' specificity (Cacioppo, Berntson, Larsen, Poehlmann, & Ito, 2000; Siegel et al., 2018). These results have been interpreted in line with the constructionist view of emotion (or the population hypothesis) (Barrett, 2017b) – which perceives emotional categories as conceptual categories (Barrett, 2017a)

Table 1. Description of psychophysiological measures

Group		Measure	Definition
Electrodermal system			
	Tonic measures		
		Skin conductance level (SCL)	Tonic level of electrical conductivity of skin
	Phasic measures		
		Change in SCL	Gradual changes in SCL measured at two or more points in time
		Frequency of NS-SCRs	Number of SCRs in absence of identifiable eliciting stimulus
		SCR amplitude	Phasic increase in conductance shortly following stimulus onset
		SCR latency	Temporal interval between stimulus onset and SCR initiation
		SCR rise time	Temporal interval between SCR initiation and SCR peak
		SCR half recovery time	Temporal interval between SCR peak and point of 50% recovery of SCR amplitude
		SCR habitation (trials to habituation)	Number of stimulus presentations before two or three trials with no response
		SCR habituation (slope)	Rate of change of ER-SCR amplitude
Cardiovascular system			
	Electrocardiogram		
		Heart rate (HR)	Temporal interval between successive R spikes
		SDNN	Standard deviation of the normal beat to normal beat intervals (normal-to-normal or NN)
		RMSSD	Root Mean Square Successive Difference) statistic
		Low Frequency (LF)	Power in low-frequency range. Mixture of sympathetic and parasympathetic rhythms
		High Frequency (HF)	Heart rate fluctuations occurring within the respiratory frequency band - Power in high-frequency range
		Respiratory sinus arrhythmia (RSA)	Respiratory gating of autonomic control by afferent input from lung stretch receptors
	Blood Pressure		
		Systolic	Systolic Blood Pressure
		Diastolic	Diastolic Blood Pressure
		Finger Temperature	
Respiratory system			
		Respiratory rate	Number of breaths
Facial system			
	EMG		
		Corrugator Supercilii	Group of facial muscles associated with frowning
		Zygomaticus Major	Group of facial muscles associated with smiling

2. Methods

2.1. The current work

The goal this work was to aggregate the results of experimental studies investigating the ANS (cardiovascular, electrodermal and respiratory) correlates of emotion elicitation. For this purpose, due to their increased complexity and dynamic nature, audiovisual stimuli (*i.e.,* videos) are thought to provide a richer and ecologically valid methodology to induce affective sates (Baumgartner, Esslen, & Jäncke, 2006). In addition, video clips typically induce a more sustained affective state compared to presentation of static stimuli that elicit only short-lived affective responses (Bos, Jentgens, Beckers, & Kindt, 2013; Gross & Levenson, 1995). As such, we restricted our meta-analytic investigation to experiments using videos to elicit any affective response. It was also our goal to assess these correlates, using different perspectives of emotional processing – through the lens of a classic view – looking at the ANS correlates of main emotional categories (including: sadness, disgust, fear, anger and happiness), but also from a dimensional perspective – namely the valence–arousal model (Russell, 1980) – which postulates a bipolar valence dimension ranging from positive to negative, and an orthogonal arousal dimension ranging from low arousal to high arousal. For the latter aim, we associated the pooled effect-size for each emotional contrast with the variance of self-reported levels of arousal, for emotional content with positive and negative valence.

2.2. Data sources

The systematic review was implemented following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & Group, 2009). The literature search was performed in multiple online databases, on August 2017, including PubMed, PsycInfo and Google Scholar, to identify relevant studies in the context of autonomic nervous system correlates of emotional processing. The following keywords and logical aggregations were used: (autonomic OR peripher*) AND (emotion OR arousal OR valence) AND (films OR movies OR clips OR videos). In addition, studies citing validated sets of emotional films were also included (Carvalho, Leite, Galdo-Álvarez, & Gonçalves, 2012; Gilman et al., 2017;

Gross & Levenson, 1995; Hewig et al., 2005; Jenkins & Andrewes, 2012; Kaviani, Gray, Checkley, Kumari, & Wilson, 1999; Maffei et al., 2014; Philippot, 1993; Ray, 2007; Samson, Kreibig, Soderstrom, Wade, & Gross, 2016; Schaefer, Nils, Sanchez, & Philippot, 2010). Last, we also screened the reference list from relevant reviews on the field. Studies obtained from more than one database were identified as duplicates. References from relevant manuscripts were also included. The selection of individual studies was conducted in two consecutive phases: screening and full-text assessment. The inclusion criteria for each phase is described below.

2.3. Inclusion criteria

For the screening phase, the following criteria was established to determine study selection: (1) the study was published as an original research article in a peer-reviewed journal – *i.e.,* reviews, commentaries, protocols, publications in book chapters or conferences were not considered; (2) the study was published in English language; (3) the study involved human subjects; (4) the study implemented the visualization of films with emotional content; (5) one or more measures of autonomous nervous system correlates were obtained. The studies meeting these criteria were comprehensively assessed during the full-text assessment phase, in which the following inclusion criteria were defined: (1) the study presents results for healthy individuals; (2) films were classified according to one specific emotional category or one specific emotional valence – *i.e.,* studies implementing mixed emotional content were not included; (3) the study summarizes results for individual peripheral measures (*i.e.,* not composites of two or more measures) and in response to one single film or one single category (*e.g.,* average of peripheral response to films from the same emotional category); (4) the study presents the results of peripheral measures, contrasting emotional films to either an emotional film with neutral content or to a baseline period.

2.4. Data extraction

A structured database was constructed to aggregate the characteristics retrieved from individual studies, including sample characteristics (sample size, participants' mean age, proportion of male/female participants), description of ANS measures, stimuli-related variables

(length of film clips, emotional category/valence of each stimulus). In addition, we also extracted valence and arousal ratings, assessed with the self-assessment manikin (SAM) (Bradley & Lang, 1994) or, alternatively, by assessing the intensity of the target emotions, as measured through the Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) or similar structured or non-structured questionnaire forms. Self-reported scores were normalized, considering the lower and upper limits of the measurement scale to allow for between-studies' comparison.

When the relevant statistics were not available from the main text, tables or supplementary information, but was represented in plots, we used the GetData graph digitizer tool (Fedorov, 2008) to extract mean and dispersion measures, based on the manual definition of axes scaling. Similar strategies have been previously described and revealed the validity of this approach to estimate real values (*e.g.,* Kalluri, Zhang, Caritis, & Venkataramanan, 2017).

2.5. Data analysis

Separate meta-analyses were conducted for each emotional category/dimension and peripheral measure. For each individual study, average scores and dispersion measures were used to compute effect sizes. To estimate within-subjects' standardized effect sizes, the mean difference between an emotional condition and neutral/baseline scores was calculated. If not directly reported, the standard deviation (SD) for difference was estimated, considering the individual SDs for each measure, *i.e.,* based on the individual dispersion values for the emotional category and the baseline/neutral condition, according to:

$$SD_{diff} = \frac{\sqrt{{SD_{cond1}}^2 + {SD_{cond2}}^2}}{2}, (1)$$

where SD_{diff} corresponds to the standard deviation of the difference. Cohen's d and confidence intervals from individual studies were aggregated using random-effects models (restricted maximum-likelihood), which constitutes a more conservative approach, to account for significant between-studies' heterogeneity. For each emotional contrast, the effect size Cohen's d was computed as:

$$d = \frac{\bar{x}_{emotion} - \bar{x}_{baseline/neutral}}{SD_{diff}}, (2)$$

Effect sizes were interpreted as small (≥0.20), medium (≥0.50) and large (≥0.80) (Cohen, 1988). The variance of Cohen's d (var_d) was calculated to establish the 95% confidence interval (CI), according to the formula:

$$var_d = \frac{1}{n} + \frac{d^2}{2n}, (3)$$

Between-studies heterogeneity was estimated based on the significance of the Cochran Q test (X^2 statistic) and I^2 statistic. I^2 was calculated as

$$I^2 = \frac{Q - degrees\ of\ freedom}{Q} \times 100, (4)$$

where Q is the Cochran's statistic. Leave-one-out sensitivity analyses were conducted to assess the impact of individual studies on the overall estimated. Several strategies were implemented for assessing publication bias, including the Begg's rank correlation statistic for funnel plot asymmetry. In addition, contour-enhanced funnel plots were used which enables the consideration of the statistical significance of study estimates. Cluster-robust meta-analytic procedures were implemented to account for the statistical dependence of multiple effect sizes obtained from the same study, as these are likely to produce clusters of internally correlated effect size estimates (Pustejovsky & Tipton, 2014). Meta-regression analyses were conducted to assess the impact of sample characteristics (mean age, proportion of male/female individuals), stimuli-related [duration of the stimuli and the nature of comparison (*i.e.,* comparison of the emotional category against neutral stimuli or against a baseline period)] and self-reported variables (valence and arousal ratings) on the individual meta-analytic estimates. With the goal of assessing the adequacy of a dimensional perspective, correlation analyses were performed between the standardized mean differences (i.e., Cohen's *d* values) and scaled measures of self-reported arousal and valence, independently of the emotional category.

Statistical analysis was performed in RStudio (v3.31.1, RStudio, Boston, MA, USA). The meta-analytic pipeline was implemented using the metafor (Viechtbauer, 2010) and clubSandwich (Pustejovsky & Tipton, 2014) packages. The dataset used for the meta-analytic investigation, and the code for the analysis is available at the Open Science Framework (https://osf.io/x6vwe/).

3. Results

Fig. 1 represents the process of article selection, as a PRISMA flowchart. The literature search yielded 3445 articles. After the combination of the datasets, 636 duplicated articles were removed, resulting in a total of 2809 articles being included in the screening phase. During the screening phase, 2299 articles were excluded for not meeting the pre-defined inclusion criteria. Of the 591 articles assessed for eligibility, 288 articles were further excluded, mainly for not presenting psychophysiological data, not having emotional contrasts, or because data were not reported for individual psychophysiological measures.

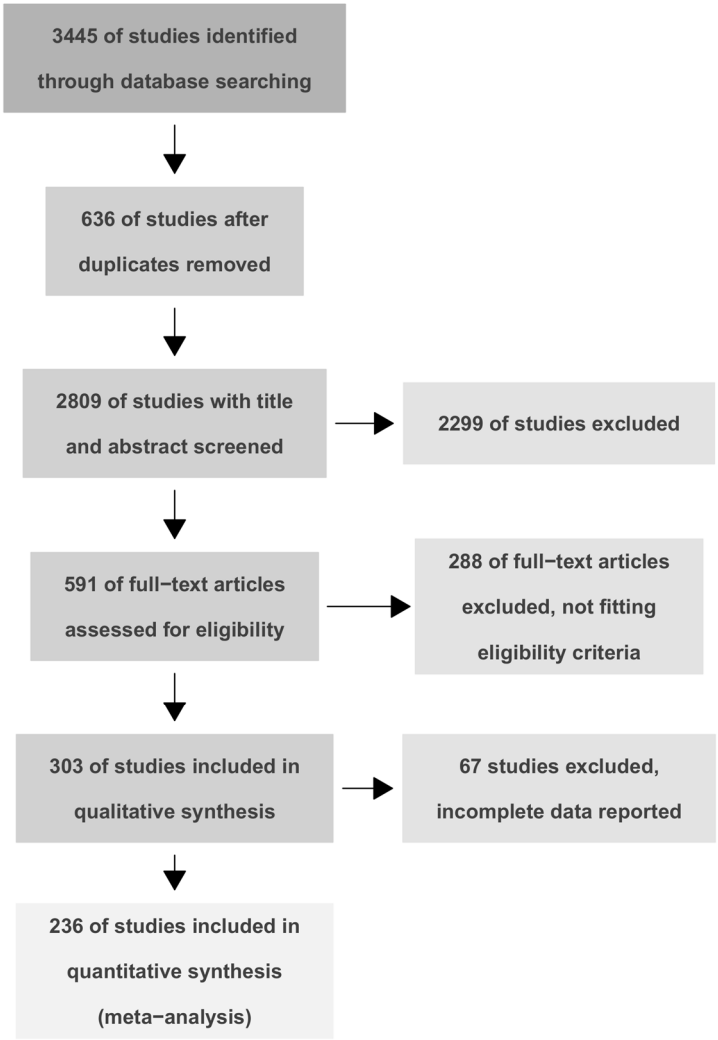

Figure 1. PRISMA flowchart

3.1. Characterization of the included studies

Table 2. Characteristics of the included studies

Author	Year	N	Country	Provenience	Mean Age	% Males
Aguado	2016	38	Spain	University	22.3	50%
Aldao	2013	17	US	University/Community	30.5	–
Anastassiou-Hadjicharalambous	2008	44	UK	Community	8.7	50%
Arnaudova	2017	78	Netherlands	University	19.6	6%
Austin	2007	11	US	Community	–	0%
Ayala	2010	20	US	Community	28.2	15%
Baldaro	2001	45	Italy	University	–	0%
Baldaro	1996	30	Italy	University	–	47%
Baldaro	1990	24	Italy	University	–	33%
Beevers	2011	67	US	University	18.4	0%
Bensafi	2004	72	US	University	12.8	50%
Berna	2014	63	France	University	20.9	0%
Blau	2009	86	Israel	kindergarten children	4.7	37%
Bogdanov	2013	21	Ucraine	University	–	48%
Bos	2013	35	Netherlands	University	20.6	34%
Bos	2013	35	Netherlands	University	20.6	34%
Bradley	2009	96	UK	Community	35.6	41%
Bradley	2007	50	US	University	19.7	44%
Bride	2014	408	US	University/Community	24.4	37%
Britton	2006	40	US	Community	19.3	48%
Brumbaugh	2013	169	US	Community	27.0	40%
Brzozowski	2017	49	UK	University	18.9	43%
Busscher	2010	36	Netherlands	Community	43.4	47%
Butler	2006	36	US	University	20.0	0%
Carboni	2017	30	Spain	University	24.8	37%
Carvalho	2012	32	Portugal/Spain	University	23.3	50%
Chentsova-Dutton	2010	34	US	Community	30.2	0%
Chentsova-Dutton	2010	60	US	University	19.4	49%
Chentsova-Dutton	2010	18	US	Community	32.1	0%
Chentsova-Dutton	2010	16	US	Community	28.4	0%
Chentsova-Dutton	2014	114	US	University/Community	21.3	35%
Clapp	2015	192	US	University	19.9	43%
Codispoti	2008	60	Italy	University	23.1	45%
Costa	2009	60	Italy	–	27.6	50%
Coyne	2011	50	UK	University	24.7	40%
Crowell	2017	116	US	Community	35.0	0%
Davis	2016	101	US	Community	5.8	54%
Davydov	2011	26	Belgium	University	20.0	0%
Davydov	2011	26	Belgium	University	20.0	0%
Davydov	2013	26	Belgium	University	20.0	0%
de Groot	2014	52	Netherlands	–	22.4	50%
de Jong	2011	60	Netherlands	University	21.6	13%
de Sousa	2012	25	Australia	Community	29.0	56%
de Wied	2012	32	Netherlands	Community	13.8	100%
Demaree	2004	52	US	University	18.5	48%
Demaree	2005	69	US	University	19.3	48%
Deng	2017	110	China	University	21.2	28%
Deng	2016	79	China	Community	20.9	39%
Eberhardt	2016	17	Germany	University	21.5	0%
Eisenberg	1992	117	US	School	7.3	56%
Elices	2012	30	Spain	University/Community	26.9	0%
Erisman	2010	15	US	University	24.1	50%
Evans	2013	87	UK	Community	33.1	33%
Fang	2001	62	US	University	19.7	100%
Fanti	2016	56	Cyprus	University/Community	20.5	46%
Fanti	2017	82	Cyprus	University/Community	21.0	50%
Fernández	2012	123	Spain	University/Community	29.2	26%
Fortunato	2013	273	Germany	Kindergarten	6.3	36%

Fowles	2000	92	US	Community	4.4	51%
Francis	2016	58	Australia	University/Community	23.8	26%
Fredrickson	1998	72	US	Community	–	50%
Gatzke-Kopp	2014	209	US	kindergarten children	6.0	63%
Gentzler	2009	65	US	Community	7.9	54%
Gilbert	2016	83	US	Community	19.7	0%
Gilchrist	2016	60	UK	University/Community	22.0	75%
Gilchrist	2016	42	UK	University/Community	22.0	26%
Giuliani	2008	16	US	University	18.8	0%
Glissen	2008	78	Netherlands	Community	3.8	49%
Glissen	2008	92	Netherlands	Community	7.4	47%
Glissen	2007	78	Netherlands	Community	3.9	49%
Golland	2015	78	Israel	University	–	0%
Golland	2014	27	Israel	University	20.0	33%
Gomez	2005	73	Germany	University	24.0	51%
Gomez	2009	76	Germany	University/Community	24.0	51%
Gračanin	2007	65	–	University	21.5	22%
Gross	1998	40	US	University	21.0	50%
Gross	1993	43	US	University	19.3	100%
Gross	1994	150	US	University	19.1	0%
Gruber	2011	24	US	Community	35.5	50%
Gruber	2011	31	US	University	20.4	35%
Hagenaars	2014	50	Netherlands	University	21.0	0%
Hamilton	2011	19	US	Community	24.4	0%
Harrison	2000	30	UK	University	21.0	50%
Hastings	2009	215	US	Community	13.3	51%
Hastings	2014	220	US	Community	13.7	50%
Hendriks	2007	60	Netherlands	University	20.4	0%
Herring	2011	39	US	University	21.5	31%
Herring	2011	39	US	University	21.5	31%
Hsieh	2016	34	Taiwan	University	22.0	18%
Ivonin	2015	23	Spain	University	27.8	57%
Ivonin	2015	25	Netherlands	University	24.0	52%
Jang	2015	20	Korea	University	21.0	50%
Jin	2015	25	US	Community	31.0	40%
Jones	2014	20	US	Community	3.1	75%
Jones	2014	21	US	Community	5.9	52%
Jönsson	2008	30	Sweden	University	23.3	50%
Kalvin	2016	169	US	kindergarten children	5.6	66%
Kaviani	2010	16	UK	Community	28.3	50%
Kaviani	2005	16	Iran	University	27.4	50%
Kaviani	2006	20	Iran	Community	–	100%
Kindt	2005	50	Netherlands	University	20.7	30%
Kornreich	1998	14	Belgium	Community	–	–
Krahé	2011	303	Germany	University	23.8	71%
Kreibig	2007	34	US	University	21.0	44%
Kreibig	2011	32	US	University	20.9	47%
Kreibig	2013	43	US	University	20.8	0%
Kreibig	2015	48	US	University	20.7	0%
Kuijsters	2016	15	Netherlands	University	22.4	53%
Kuijsters	2016	15	Netherlands	University	22.4	53%
Kuijsters	2015	38	Netherlands	Community	78.8	50%
Kumari	2001	10	UK	Community	–	30%
Kunzmann	2005	48	US	Community	21.0	50%
Kunzmann	2005	47	US	Community	71.0	51%
Kunzmann	2005	48	Germany	Community	23.9	50%
Kuo	2009	20	US	Community	23.3	0%
Kuo	2013	20	Canada	Community	23.3	0%
Kuypers	2017	80	Netherlands	University	22.5	50%
Kyranides	2016	82	Cyprus	Community	20.0	51%
Laan	1995	49	Netherlands	University	22.3	0%
Lackner	2014	48	Austria	University	21.0	0%
Lane	2009	12	US	Community	23.3	0%
LeBlanc	2016	26	US	Community	38.7	27%

Lee	2009	80	Korea	University	20.8	46%
Lin	2017	50	Israel	Soldiers	18.9	100%
Llera	2014	95	US	University	19.0	28%
Lobbestael	2006	64	Netherlands	University (7 were not)	23.4	50%
López-Benítez	2017	31	Spain	University	21.1	19%
López-Benítez	2017	33	Spain	University	21.1	39%
Maras	2012	19	UK	–	37.1	83%
Marsh	2007	23	US	Community	10.5	100%
Matsunaga	2009	12	Japan	–	–	100%
Matsunaga	2008	11	Japan	University	–	50%
Merrifield	2014	72	Canada	University	18.9	39%
Mohino-Herranz	2015	40	Spain	University	–	70%
Montoya	2005	32	Spain	–	26.0	63%
Morawetz	2016	23	Germany	–	23.0	35%
Musser	2013	75	US	Community	7.6	49%
Olatunji	2015	95	US	University	19.0	24%
Pallavicini	2013	34	Italy	University	21.2	–
Palomba	2000	46	Italy	University	23.8	33%
Pang	2013	207	US	Community	9.9	–
Park	2013	12	Korea	University	20.0	50%
Park	2011	20	Korea	University/Community	29.3	50%
Pfabigan	2015	15	Austria	Community	35.6	100%
Pichon	2014	25	–	–	23.2	48%
Pu	2010	136	US	University	18.8	49%
Quas	2007	109	US	Community	6.1	51%
Radstaak	2011	110	Netherlands	University	21.1	13%
Ramos	2015	70	Spain	University	31.7	–
Renshon	2015	138	US	University	22.8	100%
Reynaud	2012	33	France	Community	27.5	12%
Rickard	2004	21	Australia	University	25.5	57%
Rimes	2016	80	UK	Community	33.0	29%
Rimm-Kaufman	1996	32	US	University	20.0	0%
Rimm-Kaufman	1996	32	US	University	–	0%
Ripley	2017	184	US	University	19.9	45%
Ritz	2010	25	Germany	Community	28.0	36%
Ritz	2013	20	US	University/Community	27.7	18%
Ritz	2012	14	US	Community	36.4	72%
Ritz	2005	14	Germany	Community	36.4	29%
Ritz	2011	14	America	Community	36.4	29%
Ritz	2010	25	Germany	University/Community	28.0	36%
Ritz	2011	14	US	Community	36.4	29%
Roberts	2008	160	US	University	20.8	40%
Robinson	2007	55	US	University	19.1	47%
Rohrmann	2008	89	Germany	University	27.9	53%
Rohrmann	2008	89	Germany	University	27.9	53%
Rohrmann	2009	120	Germany	University	25.5	100%
Rommel	2015	24	France	University	19.0	0%
Rosselló	2015	30	Spain	Community	48.1	0%
Roth	2014	33	Israel	University	24.9	40%
Rottenberg	2003	31	US	–	33.5	0%
Rottenberg	2002	33	US	Community	32.3	30%
Rushby	2013	25	Australia	Community	31.0	56%
Salters-Pedneault	2007	37	US	University/Community	26.7	0%
Sarlo	2008	17	Italy	University	22.7	0%
Schaich	2013	66	Netherlands	University	20.1	0%
Schallcross	2017	142	US	University/Community	22.1	30%
Schmeichel	2006	50	US	University	18.9	46%
Schneider	2012	28	Germany	Community	34.7	54%
Schneiderman	2011	112	US	University/Community	23.4	51%
Schröder	2015	16	Germany	Community	30.2	81%
Seeley	2016	76	US	University/Community	26.6	41%
Seider	2011	76	US	Community	25.4	49%
Seider	2011	73	US	Community	43.7	49%
Seider	2011	73	US	Community	64.6	47%

Shenhav	2014	80	US	University/Community	27.1	51%
Shenhav	2014	80	US	University/Community	27.1	51%
Sheppes	2009	45	Israel	University	22.9	0%
Shi	2017	48	China	University	23.5	48%
Silvestrini	2007	43	Switerzland	University	24.0	84%
Simon	2017	20	US	Community	27.9	19%
Simon	2017	20	US	University/Community	27.2	15%
Šolcová	2017	124	Czech Republic	University	22.5	41%
Soto	2016	59	US	University/Community	19.5	46%
Stange	2017	134	US	University	21.9	42%
Stephens	2010	49	US	University	19.3	45%
Stoléru	1999	8	France	University	23.0	100%
Svaldi	2012	17	Germany	University	22.8	0%
Svaldi	2012	17	Germany	University	22.7	0%
Tramoni	2008	13	France	Community	24.6	38%
Tsai	2000	24	US	Community	27.9	50%
Tsai	2000	24	US	Community	75.7	50%
Tsai	2000	24	US	Community	26.7	50%
Tsai	2000	24	US	Community	73.6	50%
Tuck	2017	117	New Zealand	Community	41.8	40%
Tull	2007	17	US	University	22.0	12%
Tull	2010	34	US	University	25.9	100%
Uy	2013	7	US	Community	29.8	43%
Valiente	2004	157	US	School	7.7	53%
van den Broek	2009	24	Netherlands	Community	43.0	17%
Vasilev	2009	69	US	Community	9.8	–
Vianna	2006	16	US	15.88 (0.33)	26.7	44%
Wang	2013	98	China	University	20.0	21%
Wegerer	2013	66	Austria	University	23.4	0%
Wegerer	2013	66	Austria	University	23.4	0%
Wegerer	2014	37	Austria	University	23.9	0%
Wen	2014	27	China	University	20.0	33%
Werner	2007	16	California	Community	67.0	84%
Werner	2015	29	Austria	University	23.6	0%
Werner	2015	29	Austria	University	23.6	0%
Wittling	1998	45	–	–	–	24%
Wolgast	2011	94	Sweden	University	27.4	49%
Wu	2014	8	Belgium	University	–	63%
Wu	2014	8	Belgium	Community	–	53%
Yaroslavsky	2013	75	US	Community	29.6	0%
Yaroslavsky	2013	94	US	Community	29.0	26%
Yaroslavsky	2016	161	US	Community	16.5	64%
Yaroslavsky	2014	170	US	Community	30.9	–
Zantinge	2017	45	Netherlands	School	4.6	82%

The characteristics of the included studies are summarized on Table 2. Most studies reported two ANS measures. Among the studies included in this review (considering all the different emotional categories/dimensions), mean HR (186 studies) was the most described measure, followed by mean SCL (135 studies), HF-HRV (98 studies), RR (53 studies), EMG (47 studies), SCR (40 studies), and FT (26 studies). The most reported emotional category was sadness (123 studies), followed by fear (67 studies), happiness (58 studies), disgust (51 studies) and anger (36 studies). Most studies were conducted in Europe (48% of the studies), and North America (42% of the studies). Sample size varied from 4 to 408 participants. Most studies recruited university samples (approximately, 54%), followed by community samples

(approximately, 28%) and by mixed community/university samples (approximately, 11%), while only about 6% of the studies assessed pediatric samples. For the studies comprised by clinical and/or psychiatric patients, only the data for healthy individuals were considered. Most studies assessed subjective measures of emotional induction, including Self-Assessment Manikin (SAM) or similar Visual-Analog Scales (VAS), Positive and Negative Affect Schedule (PANAS) or the intensity of target emotions.

3.2. Individual meta-analyses of ANS correlates

The global estimates obtained for the different meta-analyses (which are described below) are summarized on Table 3.

3.2.1. Electrodermal system

Mean SCL was significantly (with a small magnitude) increased in response to sad content, in comparison to neutral/baseline values (d=.27, p=.004, k=31) – nevertheless, the significance of these effects was lost when a cluster-robust model was conducted (d=.23, p=.077). Disgust and fear were characterized by moderate/large, significant, increases of mean SCL [d=.80 (p<.001; k=16), d=.78, (p<.001; k=14)]. For happiness, there were significant, moderate [d=.70 (p=.027; k=10) overall effects across studies. Combining all the categories with negative valence together, there were moderate increases of mean SCL (d=.46, p<.001, k=87). The SCL correlates for the different emotional categories are summarized as forest plots on Fig. 2. The results of the meta-regression analysis indicated that the use of baseline vs neutral stimuli as the control category did not produce significant effects on the overall estimates (b=0.17, SE=.194, p=.378) self-reported arousal had a significant impact on the pooled estimates for sadness (b=3.33, SE=.98, p<.001). In addition, there were no effects of age on the pooled estimates (b=0.003, SE=.007, p=.636). Lastly, there was no evidence for a statistical impact of the proportion of male individuals on the meta-analytic effects for sadness (b=.168, SE=.696, p=.711). For the remaining pooled estimates, it was only possible to retrieve the information for self-reported arousal for seven or less studies, which precluded us to compute reliable meta-regression estimates for these emotional categories.

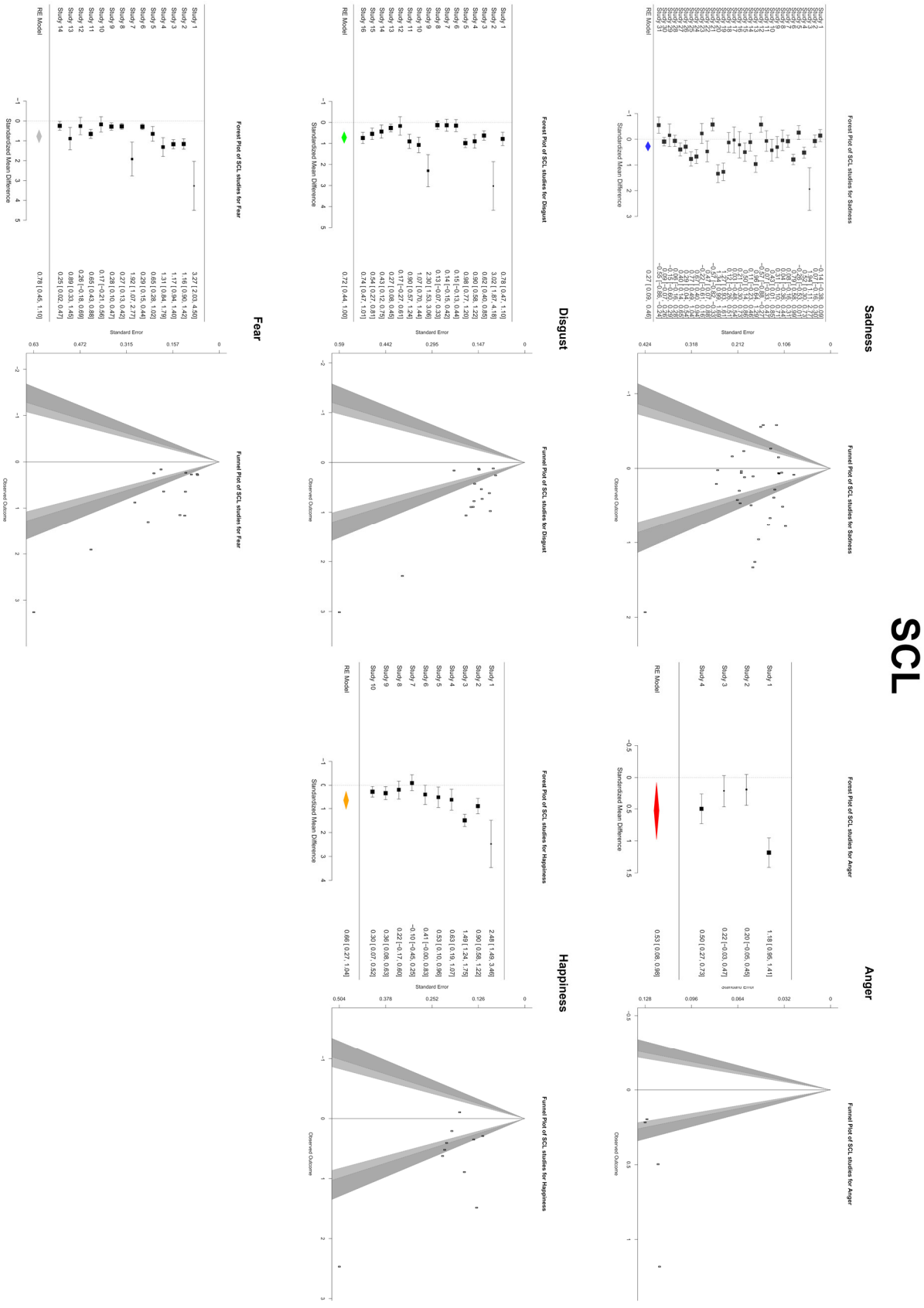

Figure 2. Forest and funnel plots for SCL correlates of the different emotional categories. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript.

Table 3. Summary of the pooled estimates

		k	Pooled ES	Lower CI	Upper CI	I^2	Cluster-Robust ES	p-value
SCL								
	Sadness	31	0.27	0.09	0.46	91.709	0.23	0.08
	Disgust	20	0.942	0.58	1.31	97	0.76	<.001
	Fear	16	1	0.57	1.3	95.7	0.775	<.001
	Anger	4	0.53	0.076	0.98	92.95	0.528	0.11
	Happiness	10	0.66	0	1.04	91.79	0.7	0.027
	Negative	87	0.48	0.36	0.59	92.64	0.452	<.001
SCR								
	Sadness	7	0.42	0.1	0.74	84.51	0.42	0.04
	Disgust	4	3	-2.275	8.7	99.85	3.21	0.33
	Fear	6	3.11	-1	7.089	99.8	3.11	0.18
	Anger	4	0.24	-0.17	1	82.044	0.24	0.34
	Happiness	5	0.75	0.08	1.42	94	0.751	0.09
	Negative	25	1.36	0.25	2.48	99.59	1	0.144
HR								
	Sadness	32	-0.042	-0.23	0.15	94.26	-0.05	0.68
	Disgust	26	0	-0.752	0.02	98.19	-0.39	0.09
	Fear	17	0.14	0	0.547	97.96	0.14	0.52
	Anger	16	0.46	-0.06	1	98.568	0.46	0.1
	Happiness	28	-0.25	-0.51	0.01	95	-0.245	0.09
	Negative	96	-0.13	-0.68	0.42	99.74	0	0.773
HF-HRV								
	Sadness	9	1.483	-2.12	5.09	99.93	1.48	0.44
	Disgust	6	0	-0.427	0.27	86.22	-0.08	0.66
	Fear	8	-0.36	-1	0.148	97.12	-0.36	0.21
	Anger	2	-0.59	-0.96	0	29.752	-0.59	0.2
	Happiness	6	-0.16	-0.53	0.21	87	-0.163	0.42
	Negative	26	0.19	-0.85	1.23	99.76	0	0.116
RR								
	Sadness	6	0.312	-0.28	0.9	96.17	0.31	0.35
	Disgust	6	1	-0.876	2.72	99.52	0.92	0.36
	Fear	5	0.19	0	0.385	61.36	0.19	0.11
	Anger	3	0.22	0	0	57.89	0.22	0.18
	Happiness	7	0.47	0.08	0.86	90	0.485	0.09
	Negative	20	0.44	-0.08	0.97	98.74	1	0.139
EMG-Cor								
	Positive	15	0.27	-0.06	0.6	92.05	0.189	0.51
	Negative	12	0.88	0.5	1.263	91.46	1	0.01
EMG-Zyg								
	Positive	7	2.035	0.74	3	98.35	2.31	0.02
	Negative	9	0	-0.6	0.15	91.15	-0.24	0.378
FT								
	Positive	5	-0.42	-1.29	0.439	90.27	-0.57	0.33
	Negative	13	-0.12	-0.28	0	77.44	-0.12	0.335

The number of SCRs was significantly increased for sadness (d=.42, p=.040, k=7) and happiness (d_{Ha}=1.00, p_{Ha}=.044) with a moderate magnitude. The remaining emotional categories were associated with a trend (although, non-significant) for increases in the number of SCRs (d_{Di}=3.21, p_{Di}=.330; d_{Fe}=3.11, p_{Fe}=.180; d_{An}=.24, p_{An}: .340).

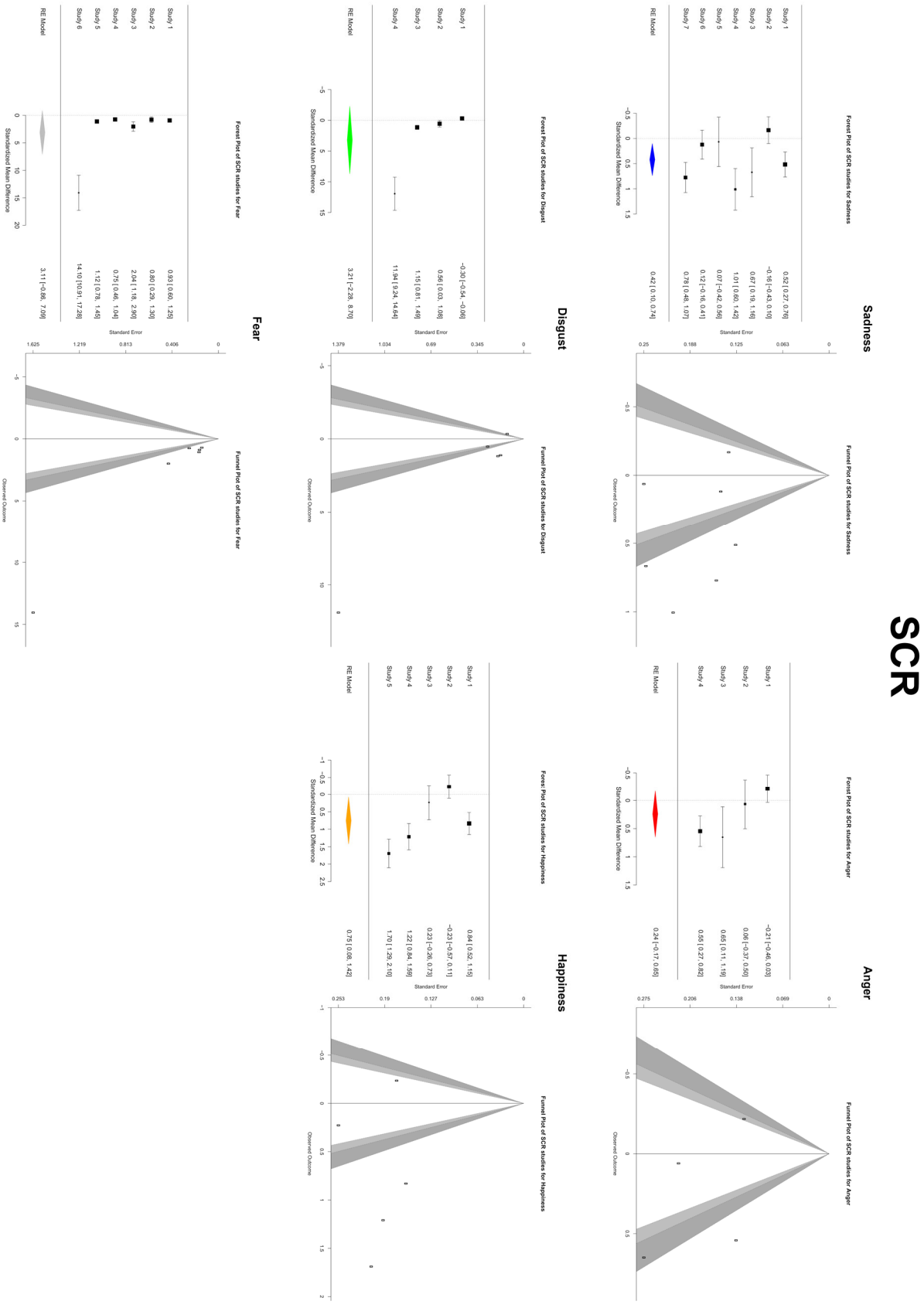

Figure 3. Forest and funnel plots for SCR correlates of the different emotional categories. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript

Nevertheless, it is important to highlight that these results should be interpreted with caution, since the number of studies reporting results for this metric ranged from four (Anger and Happiness) to seven (Sadness) studies. The combined effect of categories with negative valence did not produce significant overall effects (d=1.14, p=.157). The reduced number of studies also precluded the use of meta-regression analyses for this ANS measure (Fig. 3).

3.2.2. Cardiovascular system

Regarding the mean HR, no significant effects were noted for sadness (d=-.05, k=32). Disgust was associated with a small decrease, although non-significant, of the mean HR (d=-0.39, k=26). Anger was characterized by marginally significant increases of the mean HR (d=0.46, p=.100, k=16). Comparing with neutral/baseline stimuli, happiness was associated with small reductions of the mean HR (d=-.25, p=.090, k=28) (Fig. 4). None of the tested moderators significantly affected the pooled estimates for this metric. The combined effects of categories with negative emotional valence yielded significant, although with small magnitude, overall estimates (d=-.19, p=.038).

For high-frequency HRV, there were no significant overall effects for sadness (d=1.48, p=.440; k=9), disgust (d=-.08, p=.660; k=6), fear (d=-.36, p=.207; k=8), anger (d=-59, p=.200; k=2) or happiness (d=-.16, p=.420; k=6) (Figure 4). The combined set of negative emotional categories did not produce significant overall effects (d=-.22, p=.120). The low number of studies reporting other HRV measures, either in the time (*e.g.,* square-root of the mean squared differences, or RMSDD) or frequency domains (*e.g.,* low-frequency HRV) did not enable a meta-analytic pooling of individual studies (Fig. 5).

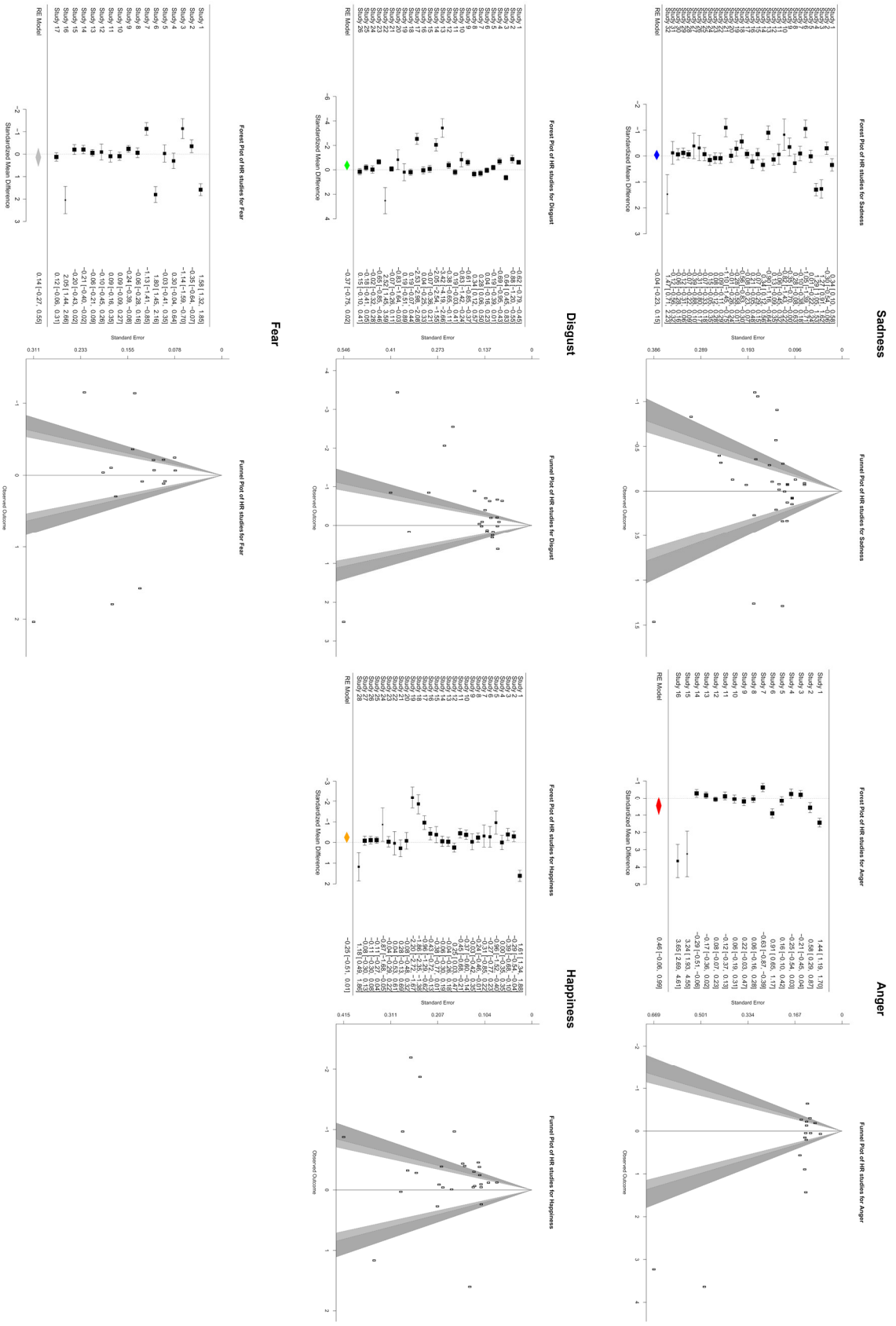

Figure 4. Forest and funnel plots for HR correlates of the different emotional categories. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript.

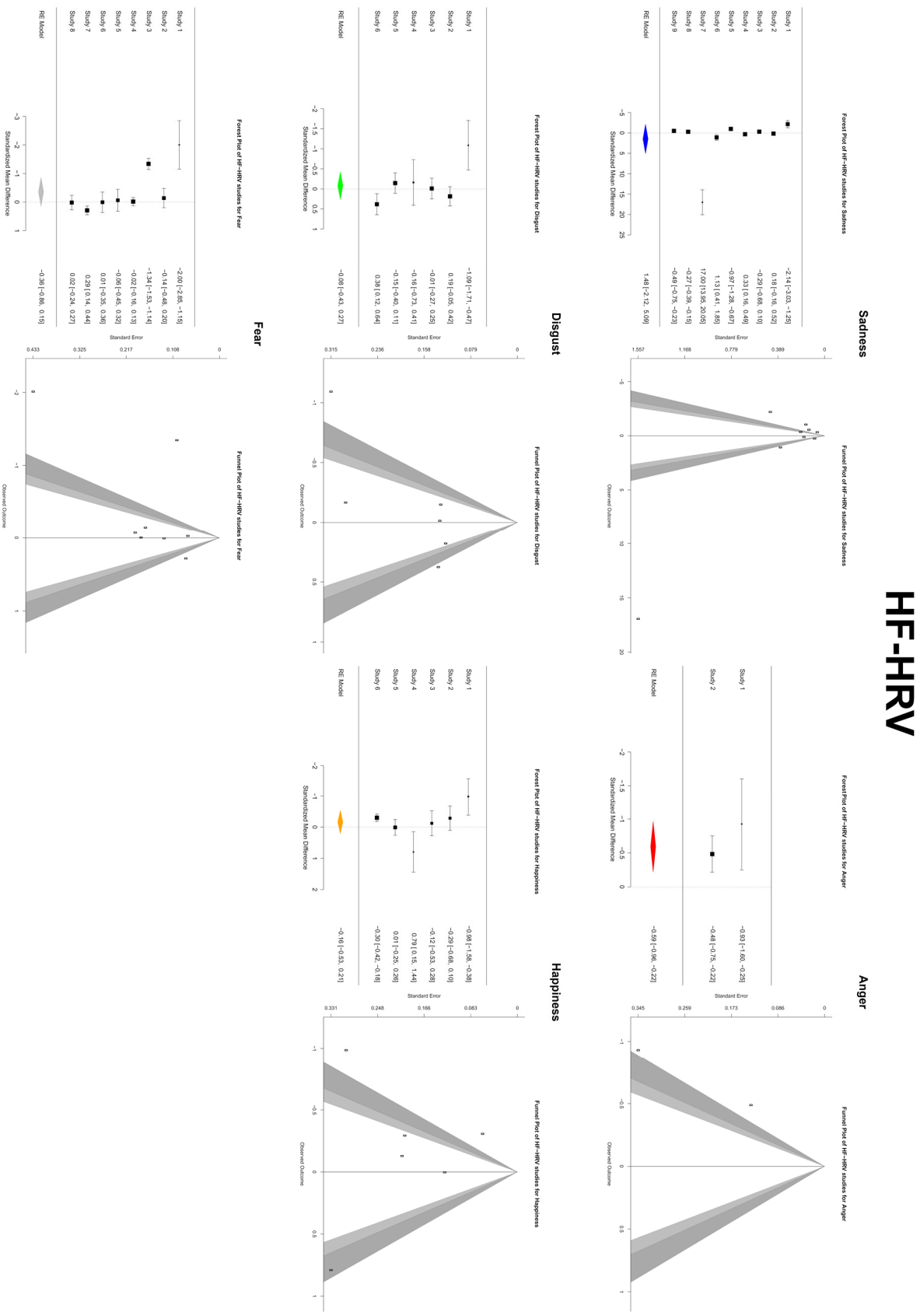

Figure 5. Forest and funnel plots for HF-HRV correlates of the different emotional categories. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript

Since there was a limited set of studies approaching the variation of finger temperature as a function of distinct emotional categories, studies were aggregated according to their emotional valence. For the set of studies with negative emotional content, there was a trend for a reduction on finger temperature (*d*=-.12, *p*=.335*; k*=13*)*. For the set of studies with positive valence, considering the very low number of studies (*k*=5) there was an overall reduction of the signal of this metric, although not statistically significant (*d*=-.57, *p*=.330) (Fig. 6).

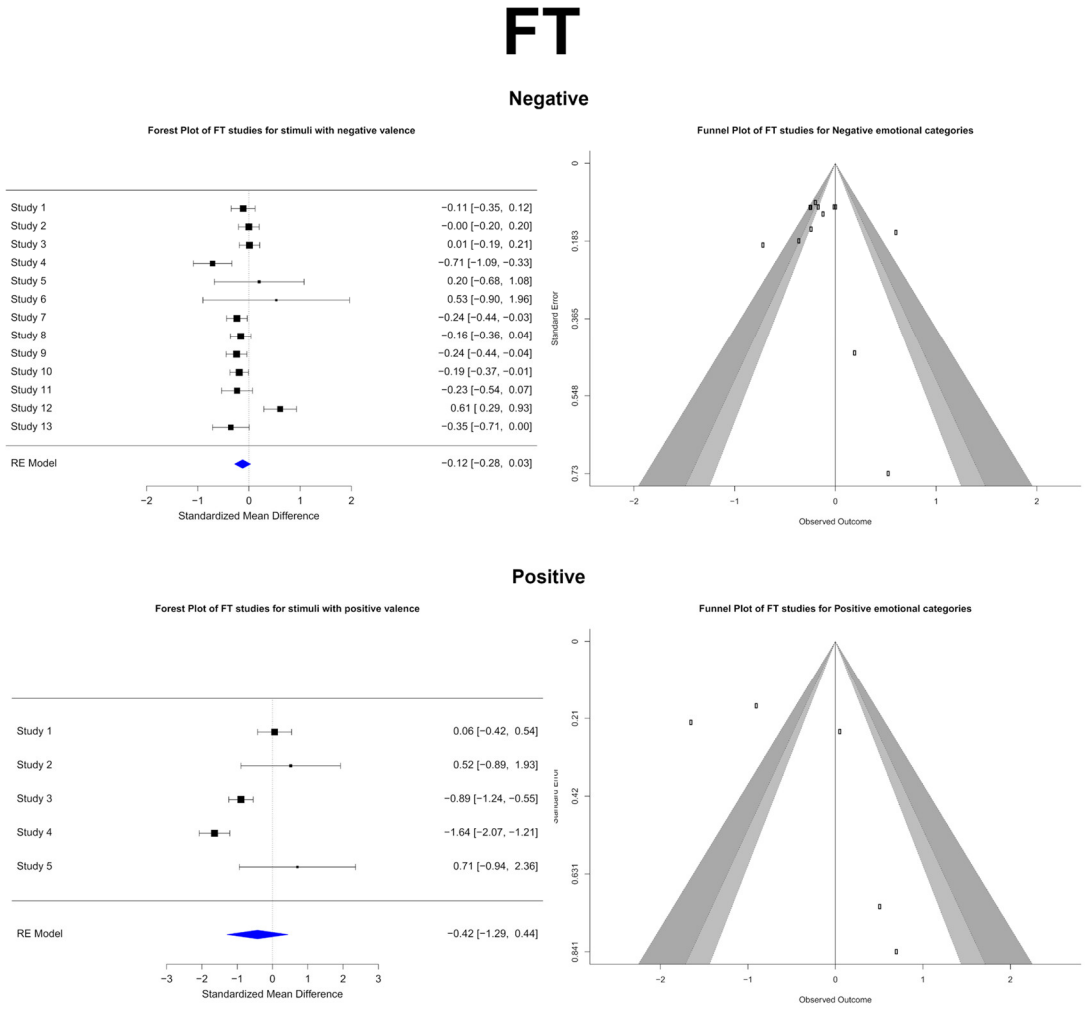

Figure 6. Forest and funnel plots for FT correlates of positive and negative valence. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript

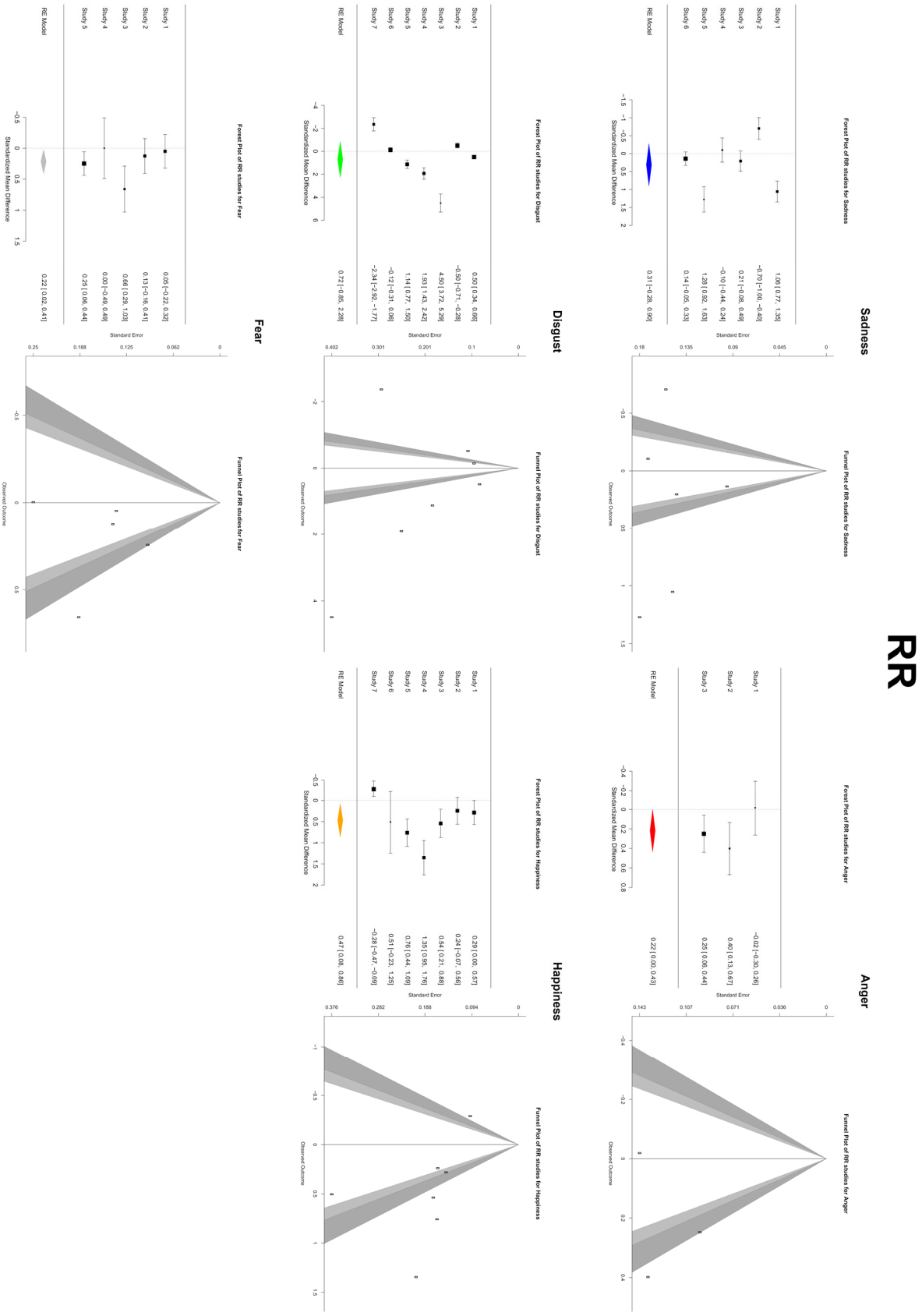

Figure 7. Forest and funnel plots for RR correlates of the different emotional categories. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript

No meta-regression aggregation was implemented for the set of cardiovascular measures, due to the reduce number of studies reporting self-reported arousal along with enough statistical information for the computation of effect-sizes. The same was also observed for the correlates of respiratory and facial systems.

3.2.3. Respiratory system

There were small-to-moderate increases in RR for happiness (*d*=.49, *p*=.090), fear (*d*=.19, *p*=.110), anger (*d*=.22, *p*=.18), sadness (*d*=.31, *p*=.35) and disgust (*d*=.92, *p*=.36) (Fig. 7). Nevertheless, none of these emotional categories was found to produce significant overall estimates. Similarly, the combined effects of the categories with emotional valence did not achieve statistical significance (*d*=.65, *p*=.139).

3.2.4. Facial system

Two EMG facial measures were considered for this meta-analytic aggregation: The Corrugator Supercilii and the Zygomaticus Major. For both measures, there was a reduced number of studies reporting essential measures for the computation of effect sizes, considering individual emotional categories. As such, we grouped the different contents according to the emotional valence of the stimuli, *i.e.,* sets of positive and negative emotions. For the set of positive emotions, non-significant changes from neutral stimulation were found for the Corrugator Supercilii (*d*=.19, *p*=.510*; k*=15); on the other hand, the set of negative emotions was associated with a significant, large, increase of the activity of the Corrugator Supercilii (*d*=1.00, *p*=.010*; k*=12). Considering the Zygomaticus Major, small, non-significant differences were obtained for the set of negative stimuli, in comparison with baseline scores (*d*=-.24, *p*=.378*; k*=9); the set of positive stimuli was characterized by significant, large increases of the Zygomaticus Major activity (*d*=2.31, *p*=.020*; k*=7) (Fig. 8).

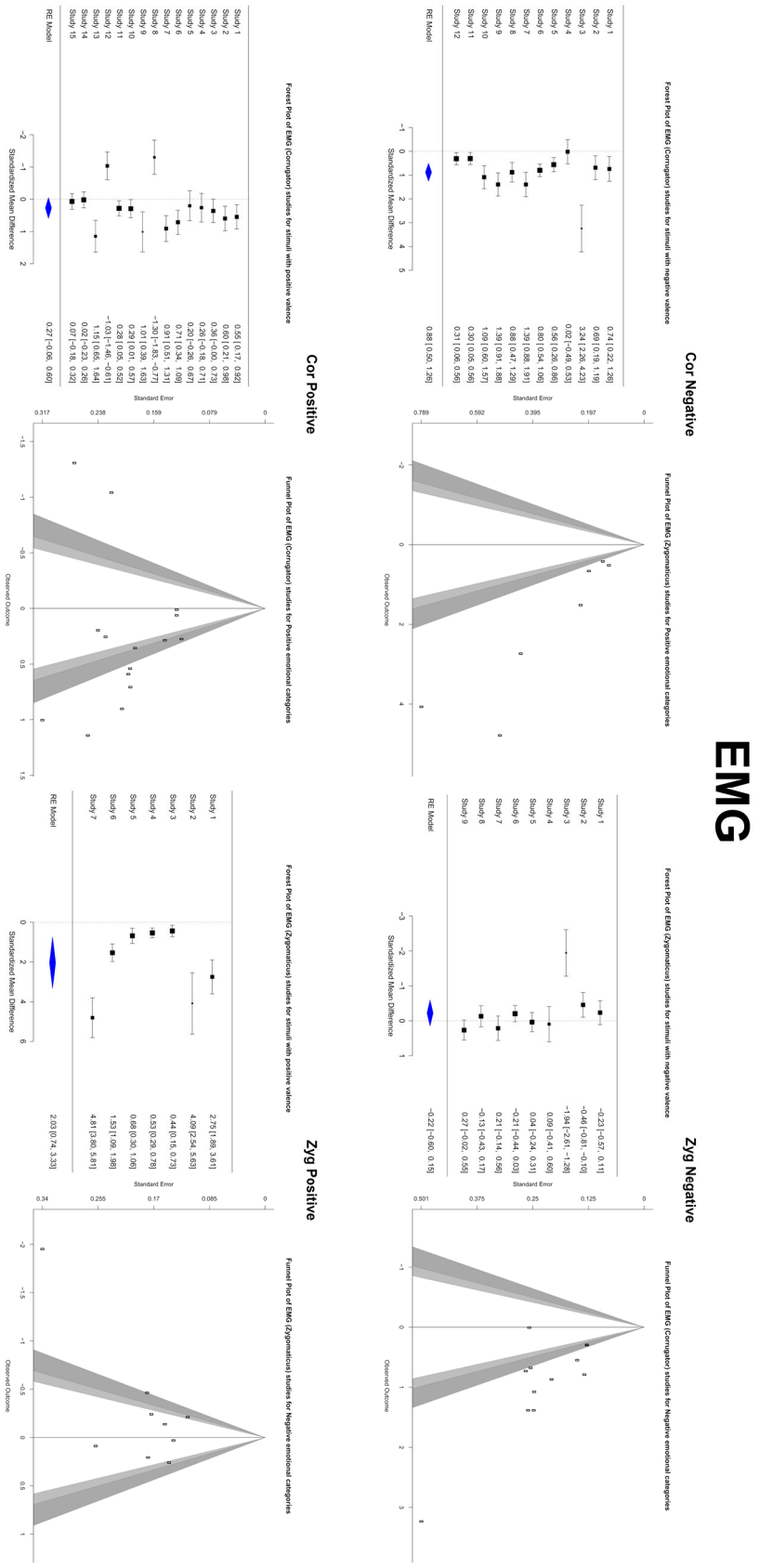

Figure 8. Forest and funnel plots for EMG correlates of positive and negative valence. The summary statistics represented in forest plots differ from the conservative cluster-robust estimates, which considers the statistical dependency between effect-sizes obtained reported on the same manuscript.

3.3. Association between ANS effect-sizes and self-reported measures of arousal

Across all the individual emotional categories, the effect size estimates of SCL were significantly associated with the self-reported measures of arousal (r=.59, p<.001). This trend was also observed for the studies examining SCR and HR, although with considerably lower magnitudes (r=0.28 and r=0.26, respectively). For studies examining RR, there was an inverse relationship between effect-size estimates and self-reported arousal (r=.34). For the remaining meta-analyzed ANS measures, we did not compute correlation coefficients, considering the reduced number of studies reporting self-reported measures together with these psychophysiological indices. The patterns association between ANS measures and self-reported arousal is visually represented on Fig. 9.

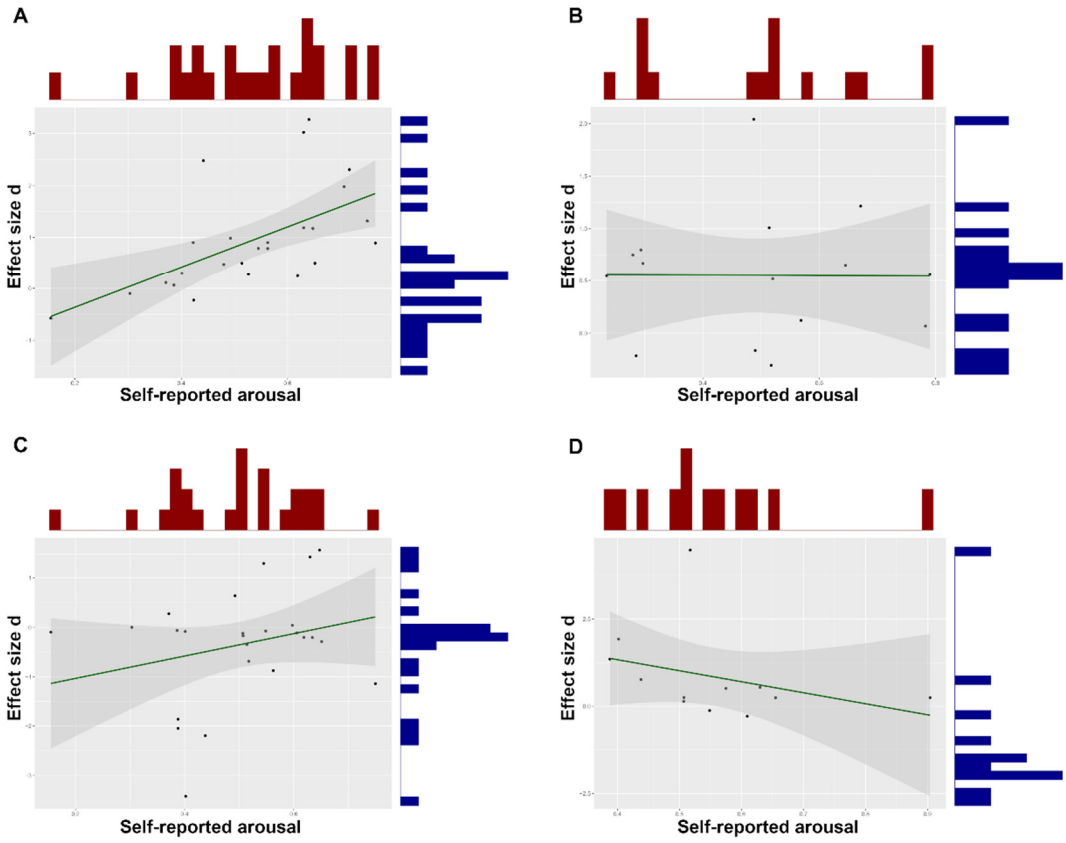

Figure 9. Scatter plots representing the association between self-reported arousal and ANS correlates for all the emotional categories, including (A) SCL, (B) SCR, (C) HR and (D) RR.

4. Discussion

In this study, we conducted a systematic review and a meta-analytic pipeline to investigate a set of ANS correlates to emotional induction. We specifically focused on audio-visual emotional induction (*i.e.,* video) strategies, with the goal of (1) yielding a more naturalistic approach of real-life emotional processing and (2) focusing on a single modality of emotional induction, to reduce inter-modalities variability. We found little evidence for the discrimination of individual categories, in comparison to stimuli of neutral valence, or baseline conditions. Nevertheless, specific ANS measures were associated with subjectively-rated arousal levels.

Dimensional approaches, which conceptualizes the affective experience as a continuum of ambiguous states of emotional processing (Posner, Russell, & Peterson, 2005), have gained cumulative acceptance among the scientific community. The most popular view within this doctrine is the circumplex model of affect (Russell, 1980), which states that any affective state results from the combination of two basic neurophysiological systems: hedonic valence (a continuum that varies from pleasure to displeasure) and arousal (a continuum that varies from calm to excited) (Russell, 2003). This meta-analytic aggregation confirms previous hypotheses suggesting that physiological responses vary incrementally with subjective ratings of valence and arousal (Posner et al., 2005). Specifically, (1) the level of subjective arousal has been demonstrated to be associated with increases of heart-rate and skin conductance (Lang, Greenwald, Bradley, & Hamm, 1993), (2) augmentation of the blood-oxygen-level-dependent (BOLD) contrast of the occipital cortex was linked to increased subjective arousal during the visualization of emotional static pictures (Bradley et al., 2003), (3) high arousal was associated with larger late positive event-related potentials (ERPs) (Rozenkrants, Olofsson, & Polich, 2008) and N170 (Almeida et al., 2016), while valence was associated with the amplitude of early to middle-range components (Olofsson, Nordin, Sequeira, & Polich, 2008). However, the magnitude of association between self-reported arousal and ANS variation varied from small to large, which raises cautious when interpreting these findings.

An important aspect that needs to be highlighted pertains to the high levels of between-studies' heterogeneity, which could not be accounted by any of the pre-defined variables of interest. This raises the possibility that some methodological aspects, including characteristics of the acquisition and processing of the psychophysiological signals may yield between-studies' differences. Having this in mind, the inclusion of structured forms for the reporting of psychophysiological signals may be an important step towards a clearer between-studies'

comparability and reproducibility. In our meta-analytic investigation, a considerable portion of the included studies did not report individual measures of central tendency and dispersion; in contrast, these measures were frequently either represented in plots or omitted, in detriment of omnibus F-statistics. When reporting between-groups' or between-conditions' comparisons, researchers tend to place an excessive focus on statistical significance, despite the limitations of this approach on the representation of the magnitude of differences (Quintana, 2017). Furthermore, as with most of psychology research, psychophysiology relies on p-values as the main source of statistical evidence (Baldwin, 2017). These practices are likely to provide overestimates of the effects' magnitude, particularly in low-powered studies (Groppe, 2017).

Following the current movements to face the reproducibility crisis, which has already been highlighted as a priority for the field of psychophysiological research (Kappenman & Keil, 2017), psychophysiology experiments would benefit from research practices that promote a comprehensive methodological description, as well as data-sharing practices that allow others to integrate the findings from multiple studies, such as meta-analytic investigations. It is our perspective that the research on this field will benefit from (1) the promotion of open-science research, namely the publication of datasets and code for processing and statistical analysis in public repositories, such as the Open Science Framework (OSF; https://osf.io/); (2) the incentive for the publication of pre-registered reports, in which the methodological protocol (including sample size determination, signal processing pipeline, analytical plan, etc.) is submitted to peer-review before the beginning of data collection; (3) the creation of online repositories/databases for the aggregation of peripheral psychophysiology investigations (following the examples of neuroimaging field, in which web-based platform allow the aggregation of multiple studies – *e.g.,* Neurosynth); (4) the development of structured checklists to enable proper and comparable reporting of psychophysiology experiments, such as the Guidelines for Reporting Articles on Psychiatry and Heart rate variability (GRAPH) (Quintana, Alvares, & Heathers, 2016).

Even though our work shares similarities with the work from Siegel and colleagues (2018), there are some notable differences that deserve to be outlined. First, we focused on the analysis of a specific modality of emotional induction – which allowed us to approximate to a more ecological fashion for emotional induction. Second, the fact that our literature search was concluded on 2017 allowed us to include a considerable wider extension of studies using the

same emotion induction modality. Therefore, we could perform a set of meta-regression analyses and to include additional ANS measures, including electromyography.

Strengths and Limitations

Despite the comprehensive approach here implemented, there are some drawbacks associated with this work. One issue pertains to the inclusion of emotional induction strategies exclusively based on films. However, with this work, we favored a deeper exploration of multiple ANS correlates of different emotional categories. Being characterized by a dynamic audiovisual nature, this modality may provide an increased ecological value on the induction of affective states. However, recent reports have questioned the notion that positive and negative feelings are mutually exclusive (Kreibig, Samson, & Gross, 2013) and that the implementation of paradigms that accommodate the co-occurrence of mixed emotional states are a most adequate representation of the multifactorial nature of emotion (Kreibig & Gross, 2017). It is relevant to emphasize that the maximum shared variance between arousal and ANS variation (namely, SCL) was, approximately, 35%. This means that 65% of the variation of SCL is not accounted by self-reported arousal. This may be due to the static evaluation of an audiovisual content, which may not accurately capture the dynamic variations of the arousal throughout its duration. The humans' ability for self-reporting their own experience is limited and often "determined" by heuristics, or shortcuts. Previous research has long demonstrated that human individuals are particularly unreliable when retrieving information from the memory of past events. People typically make their judgements based on prototypical moments, or snapshots (the most intense affective experiences) and have a difficulty in correcting for the atypicality of these moments across the overall experience – a "failure" that is known the representativeness heuristic (Kahneman & Tversky, 1972). According to this perspective, the duration of an event is typically neglected by the individual's retrieval, in detriment of a combined over-focus on the most intense timepoints (peaks) and the end of the experience, also known as the peak-the-end heuristic (Kahneman, Fredrickson, Schreiber, & Redelmeier, 1993). These constitute plausible, but theoretical explanations for the findings here reported. Complementary analyses focusing on the magnitude of the peak of skin conductance responses could better test this notion.

Altogether, we consider that future studies are required to further explore the advantages of these dynamic stimuli, by continuously assessing self-reported measures of valence/arousal or equivalent. With this strategy, researchers might be able to obtain fine-grained characterizations of different intervals of emotional films, which may contribute to a better understanding of the psychophysiological correlates of emotional induction. In addition to this, future investigations may also benefit from the combined acquisition of complementary ANS signals. This multivariate strategy may be of relevance to predict, or classify, distinct emotional states, based on the psychophysiological signatures being continuously collected.

One strength of this work concerns the fact that it tested different approaches of emotional induction. Retrieving both the categorical classification of the different stimuli and, when available, the self-reported arousal and valence ratings, allowed us to pool the effects from categorical and dimensional perspectives.

In sum, this investigation provides evidence to the perspective that individual categories of emotion are not fingerprinted in individual ANS correlates. Instead, while some ANS measures were sensitive to the valence of the stimuli (*e.g.,* EMG), measures from the electrodermal and cardiovascular system were generally sensitive to the intensity (*i.e.,* arousal) of the content being perceived. Nevertheless, the increased between-studies' heterogeneity (which had also been described in previous aggregations of psychophysiological measures) raises cautious on the interpretation of the pooled estimates.

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Supplementary Information

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

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CHAPTER 3.2

The good, the bad and the connectome: the impact of positive versus negative emotional induction on the dynamics of functional connectivity

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Manuscript in preparation

The good, the bad and the connectome: the impact of positive versus negative emotional induction on the dynamics of functional connectivity

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Abstract

During the last decades, an extensive body of scientific research has focused on assessing the neurobiological mechanisms underlying emotional processing. Neuroimaging studies – namely functional MRI studies – have primarily favored locationist approaches, *i.e.,* investigating which brain regions increase or decrease their activity during the exposure to a specific emotional condition. Because of this focus, the understanding of how whole-brain network models underlay these processes is lacking. In this study, we used a publicly available dataset to employ static and dynamic whole-brain connectome analysis during positive and negative induction conditions. We observed that both positive and negative induction are associated with statistically significant increases in static functional connectivity (FC). In addition, comparing to the positive emotional induction, negative induction is characterized by increased whole-brain FC. Regarding the dynamic FC (dFC), it was observed that there were significant within-conditions' differences in the probability of occurrence of distinct dFC states, including a state involving sensorimotor nodes, a state comprised of nodes from the orbitofrontal cortex and a third state including nodes from parietal, temporal and frontal brain regions. With this innovative approach, these findings provide novel advances regarding the complexity of emotional processing at the whole brain level.

Background

How does a human being process an emotional experience? This has been a historical hot topic in the neuroscience and psychology scientific literature. Classic theories of emotion propose that different emotional categories are associated with unique neurobiological responses. Despite the huge popularity of such view, this perspective has been criticized with the argument individual emotional categories are not uniquely processed at the central or peripheral nervous system levels. Meta-analytic aggregations of central (Lindquist, Satpute, Wager, Weber, & Barrett, 2015) and peripheral (Moreira et al., 2018) (Siegel et al., 2018) measures of the nervous system have failed to provide convincing evidence for the classic view of emotions. In contrast with this perspective, an alternative view - the circumplex model of affect (Russell, 1980) – was derived from dimension reduction and uni- and multi-dimensional scaling techniques and provided a spatial representation of the affective experience. According to this, dimensional views of emotions postulate that every emotional experience is better perceived as the combination of two bipolar, independent dimensions: the emotional arousal and the hedonic valence (Barrett & Russell, 1999). Previous reports demonstrate that self-reported arousal contributes to neurobiological responses, both with central and peripheral measures.

Most studies investigating the neurobiological correlates of emotional processing in the central nervous system have focused on locationist approaches, *i.e.,* by investigating which brain areas are preferentially activated in the presence of a given experimental condition. More contemporary perspectives have favored the study of the human brain as a network of functionally connected brain regions (Bullmore & Sporns, 2012). Such approaches can be applied either to task-independent brain activity, to study what is known as the resting-state functional connectivity (rs-FC), as well as during task-performance, where the most popular analytical strategies to assess functional connectivity typically rely on psychophysiological interactions (PPI) or dynamic causal modelling (DCM). These analytic strategies may provide rich information regarding the patterns of functional connectivity (FC) of *a priori* defined regions of interest (ROIs). However, such analyses are (at least) partially motivated by model-driven strategies, in which the researcher is interested in assessing associative or causal patterns (the latter is defined as effective connectivity, EC) between specific ROIs or between one or more ROI and the rest of the brain. Even though less frequently implemented in the context of task-dependent FC, the use of whole-brain approaches for the examination of FC may yield novel

insights regarding the network of the human brain during specific experimental conditions. In the context of traditional static functional connectivity (FC) analysis, the correlation between the blood-oxygen level-dependent (BOLD) response of segregated brain areas is computed over entire recording sessions (Sporns, Tononi, & Edelman, 2000). In this context, the use of specific analytical procedures, such as the network-based statistic (NBS), allow the identification of components of edges that differentiate groups of individuals or experimental conditions. In addition, to the best of our knowledge, no study has yet reported the characterization of FC during emotional induction, considering its temporal dynamics.

In this work, we aimed to assess how emotional induction is processed at the level of the central nervous system. Instead of focusing on a locationist view of the human brain, we intended to characterize how the emotional experience affects the complex interactions between separate brain regions at the whole-brain level, both at the static and dynamic FC levels.

Methods

Participants

The data used in this study were obtained from a publicly dataset available from the OpenNeuro dataset (K Gorgolewski, Esteban, Schaefer, Wandell, & Poldrack, 2017). This dataset contains data from 20 healthy individuals, acquired while they were performing an emotion-induction task. The task was comprised of musical and non-musical auditory stimuli with positive and negative hedonic valence. The full characteristics of the experimental apparatus are described on the manuscript reporting this dataset (Lepping et al., 2016).

Data acquisition

The imaging session was performed in a Siemens Skyra 3T. For the structural acquisition, a high-resolution T1-weighted 3D MPRAGE sequence was performed with the following characteristics: repetition time (TR) =2.300 ms; echo time (TE) = 2.01 msec, flip angle

(FA) = 9°, field-of-view (FOV) = 256 mm, matrix = 256x192, slice thickness = 1 mm. For each run of the functional acquisitions, 105 echo-planar images (EPI) were acquired using the following parameters: TR = 3.000 ms, TE = 0.025, FA = 90°, FOV = 220 mm, slice thickness = 3 mm.

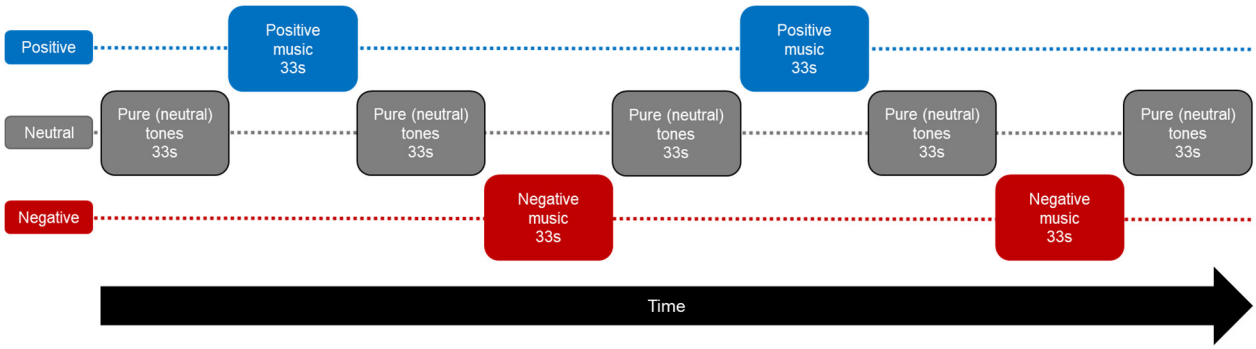

Figure 1. Overview of the experimental paradigm. Each run started with a baseline period (Pure tones) of 33s, followed by a block of emotional induction (either positive or negative; duration=33s). Until the end of the run, this scheme was repeated three times, with alternating emotional conditions.

Data processing

The MRI data preprocessing was executed using the OpenNeuro platform with the FMRIPREP workflow (Esteban et al., 2019), a Nipype (Krzysztof Gorgolewski et al., 2011) based tool. The pipeline was applied to one structural (T1-weighted, T1w) and five functional images for each subject. Skull-stripping was applied to structural images, using antsBrainExtraction.sh v2.1.0. Brain-extracted images were then normalized to the (brain-extracted) ICBM 152 Nonlinear Asymmetrical template (Fonov, Evans, McKinstry, Almli, & Collins, 2009), using a nonlinear registration with the antsRegistration tool of ANTs v2.1.0 (Avants, Epstein, Grossman, & Gee, 2008). Segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed with fast (FSL v5.0.9).

Functional data was preprocessed with the following steps: slice-timing correction with the AFNI program, motion correction using FSL *mcflirt*, co-registration to the corresponding T1w

using boundary-based registration with 9 degrees of freedom, using bbregister of Freesurfer (Fischl, 2012). Transformations for motion corrections and co-registration of the BOLD images to T1w and from T1w to the MNI template were concatenated and implemented in a single step with antsApplyTransforms (ANTs v2.1.0), using Lanczos interpolation.

CompCor (Behzadi, Restom, Liau, & Liu, 2007) was used to obtain physiological nuisance regressors, in which a principal components analysis was implemented in temporal (tCompCor) and anatomical (aCompCor) variants. A mask to exclude signal with cortical origin was obtained by eroding the brain mask, ensuring it only contained subcortical structures. Six tCompCor components were then calculated including only the top 5% variable voxels within that subcortical mask. For aCompCor, six components were calculated within the intersection of the subcortical mask and the union of CSF and WM masks calculated in T1w space, after their projection to the native space of each functional run. Frame-wise displacement (Power et al., 2014) was calculated for each functional run using the implementation of Nipype.

Data analysis

The timeseries for the preprocessed scans were extracted with *fslmeants* for different parcellation schemes, including the updated version of the Automated Anatomical Labelling (AAL) (Rolls, Joliot, & Tzourio-Mazoyer, 2015).Connectivity matrices were built for each parcellation scheme. Static functional connectivity (FC) was performed with network-based statistic (NBS) (Zalesky, Fornito, & Bullmore, 2010). This approach enables a proper control of the family-wise error rate when mass univariate testing is performed at every edge comprising a network (Figure 2). A permutation-based paired samples *t*-test was implemented to compare the connectivity matrices between segments with positive and negative emotional content. Statistical significance was defined according to an edge threshold of $p<.001$ (corresponding to a T-value of 3.92, with 18 degrees of freedom. The graphic visualization of significant networks was performed with BrainNet viewer (Xia, Wang, & He, 2013).

In addition, we focused on the characterization of the dynamical FC (dFC), by identifying recurrent FC states and comparing the probability of occurrence of each individual FC state in different experimental conditions. The approach for the characterization of dFC is fully described

in (Cabral et al., 2017). Briefly, phase coherence connectivity (BFC) (Deco et al., 2017; Deco & Kringelbach, 2016; Glerean, Salmi, Lahnakoski, Jääskeläinen, & Sams, 2012; Ponce-Alvarez et al., 2015) was used to obtain an instantaneous *NxNxT* (where N is the number of regions; and T the number of timepoints) FC matrix for each timepoint (*i.e.,* the dFC at time *t*; dFC(*t*)). BFC was calculated with the Hilbert transform. For the between-conditions' comparison over time, we considered the leading eigenvector of each dFC, which captures the most dominant connectivity pattern of dFC(*t*). In contrast with other approaches for the examination of dFC – which compare the upper triangular elements of *N*x*N* dFC(*t*) matrices obtained at each timepoint – the leading eigenvector reduces a *N(N-1)/2* to *N*, while accounting for most of its variance.

To detect individual FC patterns, a clustering analysis was applied on all the leading eigenvectors V1(*t*) across time points and subjects (*i.e.,* 525 × 19 = 9975 leading eigenvectors). Clustering was implemented with k-means, with a range of considered solutions between 2 and 20. Clustering was implemented with a squared Euclidean distance and 200 replicates. As a result, *k* cluster centroids were obtained, each being a *N*x1 vector representing a recurrent FC pattern). The optimal clustering solution was evaluated by assessing the clustering solution that yielded the most significant between-conditions' differences.

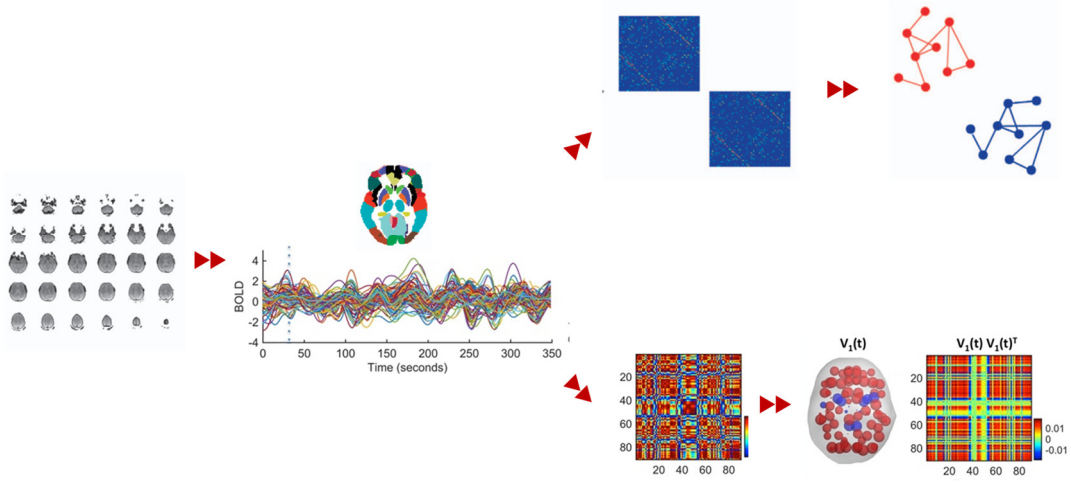

Figure 2. Summary of the analytical pipeline of task-related fMRI. After preprocessing of the functional images, the timeseries for each region (defined according to standard atlases) were extracted. For the purpose of static FC analysis, a symmetric adjacency matrix *R* was created, where each cell r_{ij} represents the correlation *r* between the time-series *i* and *j*. Pearson coefficients were converted to normally distributed *Z*-values using the Fisher's *r* to *z* transformation. Matrices were then aggregated for within-conditions' analysis. With regards to dynamic FC analysis, the phase coherence connectivity was calculated to obtain instantaneous

matrices. The leading eigenvectors (*i.e.,* the dominant pattern of FC in each instantaneous matrix) were clustered to identify recurrent FC states.

A permutation-based paired t-test was used to identify significant differences between the probability of occurrence (*i.e.,* the ratio between the number of epochs assigned to a given cluster centroid Vc and the total number of timepoints) of each FC state across different experimental conditions (*i.e.,* positive, negative and neutral). This test was implemented with 10.000 permutations of labels of experimental conditions to independently estimate the null distribution for each condition.

Results

Considering an alpha criterion of .0005, the contrast emotional induction < baseline was significantly associated with an FC network (p=.002; with 60 nodes and 111 edges), involving bilateral amygdalae, hippocampi, parahippocampi, insula, putamen. In this network, bilateral temporal pole were important nodes, with several connections, particularly with cerebellar regions. Regarding the contrast positive induction < baseline conditions was associated with a network with 109 edges (involving 67 nodes, with p=.004), mainly comprised of limbic, striatal, insular, sensorimotor, parietal, occipital and cerebellar brain regions. In addition, the contrast negative induction < baseline was associated with statistically significant increases in a network (with 10 edges and 9 nodes, with p=.038), encompassing the bilateral temporal pole, hippocampus, parahippocampus, supramarginal and fusiform gyri and cerebellum. In addition, there were decreases in the insula, olfactory and middle cingulum of the left hemisphere; and lingual gyrus, fusiform and supplementary motor area of the right hemisphere. The contrast negative>positive was associated with significant FC increases of a network with 38 edges (27 nodes, with p=.007) and comprised of edges of the occipital lobe (including cuneus, calcarine and lingual gyrus), cerebellum, angular gyrus, right putamen and inferior frontal nodes (Figure 3).

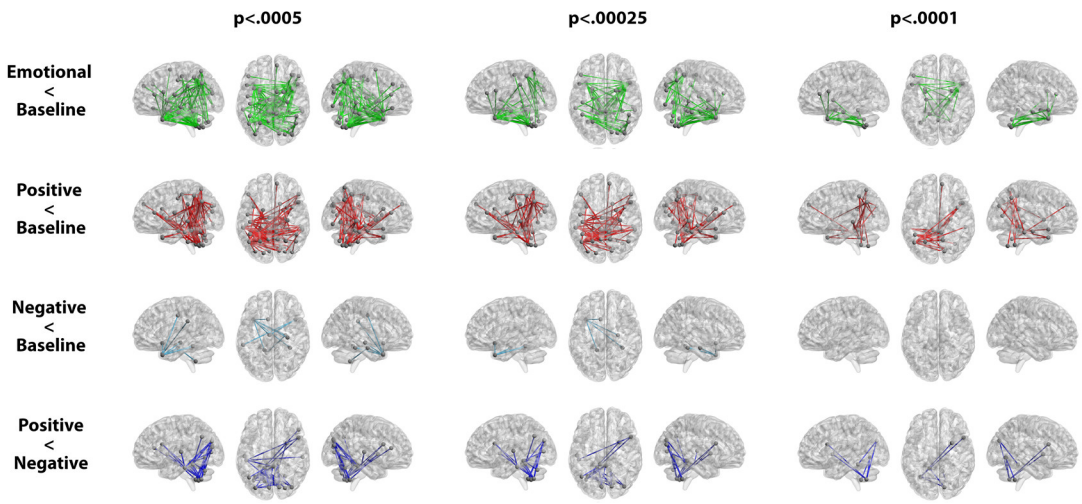

Figure 3. Networks with significantly increased FC across emotional conditions. Different thresholds are presented in separate columns (p<.0005, p<.00025 and p<.0001, from left to right).

With regards to dFC, the most prevalent FC pattern (state 1; VC_1), which occurs more than 40% of the time, corresponds to a state of global BOLD coherence (all VC_1 elements have the same sign, so the outer product, VC_1VC_1T, is non-negative). In other words, during the epochs *t* when the dFC is mainly shaped by this pattern, the BOLD signals of all brain areas exhibit a strong coherence. The remaining states were characterized by elements with different signs, suggesting that FC can be partitioned into two communities (illustrated in red and blue), with positive FC values within the community elements and negative FC values between communities (Cabral et al., 2017).

Negative emotional induction was associated with significantly decreased probability of occurrence of state 3 (p=.038, corrected for multiple comparisons) in comparison to neutral stimuli. In addition, significant differences were obtained in state 5, a network formed by edges from the sensorimotor cortex, temporal regions and striatal nodes. This FC state displayed a significantly increased probability of occurrence in the negative emotion condition in comparison to both positive (p=.017) and neutral conditions (p=.046). In addition, there were significant differences in the probability of occurrence of state 2 in the positive emotion condition in comparison to the neutral condition (p=.015). No significant differences were obtained for the remaining FC states.

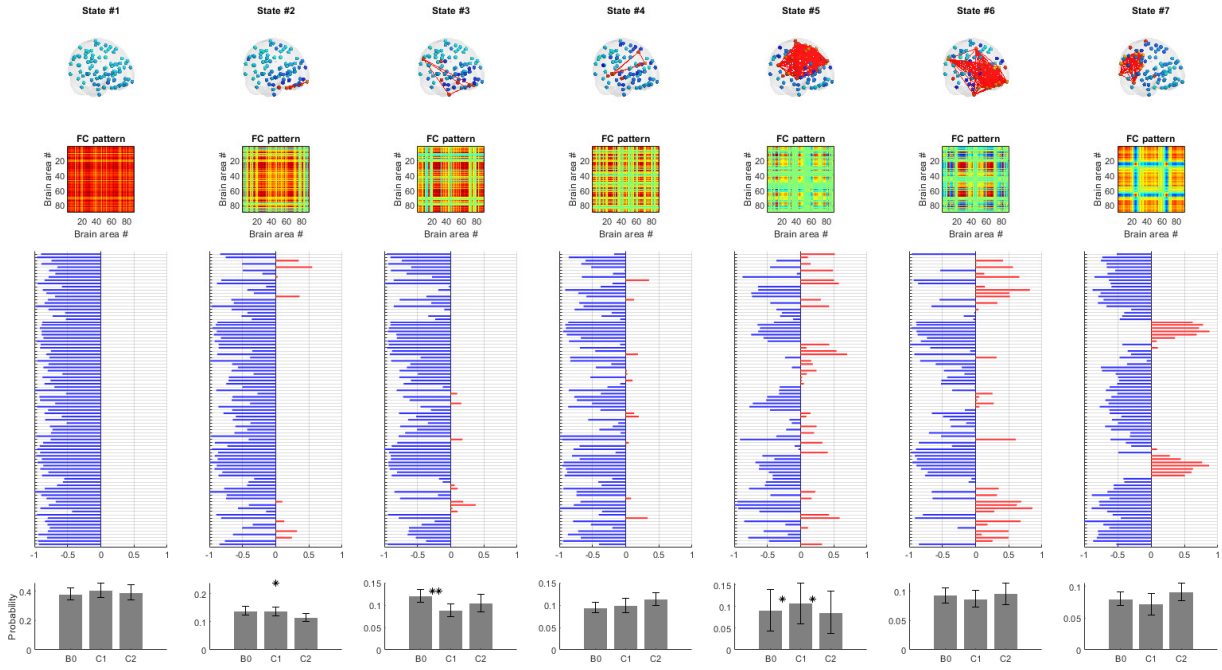

Figure 4. Dynamic FC states. A. Recurrent FC states obtained with k-means clustering. B. Distribution of each region to that state. C. Between-conditions' comparison. D. Matrices for the different FC states. FC states 2, 3 and 5 had significant differences between conditions. *p<.05 (uncorrected values); **p<.05 (corrected for multiple comparisons with Bonferroni correction).

Discussion

In this work, we implemented a magnetic resonance imaging investigation to characterize the human connectome underlying emotional processing. Using an available dataset from OpenNeuro, we analyzed the synchronization between different brain regions during the induction of negative and positive affective experiences. To the best of our knowledge, this work represents the first description of the impact of emotional induction on the repertoire of functional networks. Using this approach, we observed that a network comprised of sensorimotor, temporal and striatal nodes revealed an increased probability of occurrence during negative emotional induction, in comparison to the remaining experimental conditions. On the opposite, there was significantly decreased probability of occurrence of a lateralized network comprised of parietal, temporal and frontal nodes. A network comprised of OFC nodes was found to have a significantly reduced probability of occurrence. With regards to static FC, we observed that both positive and negative emotional induction were associated with significantly reduced

whole-brain FC. In addition, we observed that negative emotional induction is associated with significant decreases of the functional connectivity of spatially distributed networks, involving sub-cortical and posterior cortical nodes.

With respect to the network with reduced probability of occurrence during negative emotional induction, it is relevant to highlight that even though there is most to be unrevealed regarding the laterality of FC associated with emotional processing, lateralization of emotional representation has been previously reported (Berridge & Kringelbach, 2015). It has been suggested that pleasantness is particularly associated with the modulation of regions of the left hemisphere (Davidson, 2004).

The OFC has been consistently described to have a crucial role in emotional processing with a great impact on the representation of reward. (Kringelbach & Rolls, 2004). In particular, the mid-anterior division of the OFC seems to be preferentially associated with subjective pleasure, in comparison with most other limbic regions (Berridge & Kringelbach, 2015; Davidson, 2004).

A common result in our analyses pertains to the involvement of the cerebellum in the between-conditions' comparisons. The involvement of the cerebellum in emotional processing has been accumulating increasing support in the scientific literature. For instance, the cerebellum has been systematically involved in psychiatric disorders characterized by impaired emotional processing, such as major depression (Peng et al., 2011), anxiety disorders (Nakao et al., 2011) or schizophrenia (Chen et al., 2013). Lesion studies have also demonstrated that cerebellar damages result in abnormal emotional processing (Turner et al., 2007). In addition, the involvement of the cerebellum in emotional processing has been well described in functional tasks, including visual-induced emotion.

An increased auditory-sensorimotor coupling has been demonstrated in musicians (Tanaka & Kirino, 2018). Furthermore, damages to the operculum are thought to impair the emotional responses to music content (Griffiths, Warren, Dean, & Howard, 2004).

Altogether, these results suggest that stimuli with negative hedonic valence may have a more pronounced effect on whole-brain rs-FC than positive induction. Previous reports have demonstrated that negative stimuli may have stronger neurobiological responses than positive

stimuli (Mak, Hu, Zhang, Xiao, & Lee, 2009). It has also been proposed that stimuli with a negative emotional valence exert a strong influence at several behavioral domains. One such example concerns the impact of emotion on action selection during decision-making paradigms, which has for long been highlighted in the state-of-the-art (Damasio, 1994). According to such perspectives, emotional states with opposing hedonic valence may be determinant for individual choices – *e.g.,* an individual feeling anxious about the potential outcome of a risky choice may prefer the safer option; someone feeling great may be prone to donate to charity (Lerner, Li, Valdesolo, & Kassam, 2015).

An important question pertains to the complementary evidence provided by static and dynamic approaches of FC. While we verified reduced whole-brain FC during conditions of emotional induction, we noted a different picture when analyzing the temporal FC dynamics. For instance, we observed that a network comprised of sensorimotor nodes had an increased probability of occurrence during negative emotional induction.

Some limitations might be associated with this work. The NBS approach is typically implemented for assessing resting-state FC. However, we applied this strategy to compare FC networks between distinct experimental conditions. This option may be questioned by the fact that, in contrast with the typical setting of resting-state acquisitions, where people are expected to stay in a more constant state, where the external stimulation is generally absent, a connectomics approach derived from task-related acquisitions will likely be associated with a totally contrasting scenario. When people are engaged in a given experimental task, the external stimulation will vary in a variety of components, including the physical properties of the stimuli. In the case where participants are presented with music tracts, even if the whole tract is perceived as generally positive or negative, it does not mean that the level of positivity or negativity is constant across its entire extension. As such, this is something that needs to be considered when interpreting these findings. On the other hand, this is still more advantageous than presenting the task stimuli in an event-related fashion, where due to the unpredictable and non-consecutive presentation of each stimulus, the influence of this same stimulus will not be sustained. Another consideration pertains to the possibility that the results here obtained may be influenced by a variability in individual characteristics, such as personality traits or emotional regulation profiles.

Despite these questions, this investigation represents a unique characterization of the human whole-brain connectome during emotional induction. While most studies address FC based on static perspectives, this strategy does not capture the switching behavior between FC states (Hansen, Battaglia, Spiegler, Deco, & Jirsa, 2015). Thus, this work may constitute an important contribution for understanding the synchronization between different brain regions during the emotional experience.

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Chapter 4. Emotional interference in decision-making

CHAPTER 4.1

Impulsivity in the brain and the body: neuroimaging and psychophysiological correlates of the big-five facets of impulsivity

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Impulsivity in the brain: neuroimaging correlates of the big-five facets of impulsivity

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Abstract

Impulsivity is characterized by a set of behavioral patterns, such as maladaptive decision-making, lack of inhibitory control, inadequate planning, and can predispose individuals to dysfunctional psychological conditions. At the neurobiological level, impulsivity is commonly associated with structural and functional alterations of striatal-thalamic-cortical brain regions. However, the impact of different dimensions of impulsive traits on the whole-brain functional connectome is still poorly understood. In this work, we assessed the impact of different dimensions of impulsivity, as measured by the five dimensions of the UPPS-P scale (negative urgency, lack of premeditation, lack of perseverance, sensation seeking and positive urgency), on resting-state functional connectivity. We observed that lack of premeditation was significantly associated with a network involving the putamen, amygdala and cerebellum. Other dimension of impulsivity, negative urgency, was associated with the FC of a network comprising anterior, middle and posterior divisions of the cingulum, bilateral insula, cerebellum. These results provide novel evidence for the correlates of distinct impulsivity dimensions on the whole-brain FC – namely the association between impulsivity and reward and emotional-related brain networks.

Background

Impulsivity is a multifactorial trait with a normal variation across individuals. Increasing levels of impulsivity are commonly associated with maladaptive decision-making (Korponay et al., 2017), and with behavioral deficits, including lack of inhibitory control, inadequate planning and impaired performance during delay-discounting tasks (De Wit, 2009). When manifested in high levels, it may predispose individuals to a set of dysfunctional conditions, such as attention-deficit/hyperactivity disorder (ADHD) (Winstanley, Eagle, & Robbins, 2006), drug addiction (Dalley, Everitt, & Robbins, 2011), internet addiction (Weinstein & Lejoyeux, 2010), pathological gambling (Blaszczynski, Steel, & McConaghy, 1997), compulsive buying (Dell'Osso, Allen, Altamura, Buoli, & Hollander, 2008), among others.

From a conceptual perspective, even though several contributions have been proposed to integrate impulsivity in a comprehensive theory of personality, none has received a conceptual acceptance among the scientific literature, which may arise from disagreements on personality dimensions across distinct models (Whiteside & Lynam, 2001). In an attempt to overcome this limitation, the original version of the UPPS was developed in line with the Five-Factor Model of personality, which is comprised of five higher-order dimensions: neuroticism, extraversion, openness to experience, agreeableness and conscientiousness (Costa Jr & McCrae, 1990). The resulting instrument was comprised of four subscales: negative urgency: tendency to act rashly under extreme negative emoticons; lack of premeditation: tendency to act without thinking; lack of perseverance inability to remain focused on a task; sensation seeking: tendency to seek out novel and thrilling experiences (Whiteside & Lynam, 2001). Later, it was recognized that impulsive action under positive emotions exists resulting in the development of a positive urgency scale which was added to the UPPS scale resulting in a final list of 59 items (Cyders et al., 2007).

With regards to the neurobiological level, previous studies with human and animal models have demonstrated that impulsivity is associated with the availability of dopamine receptors and midbrain auto-receptor binding and dopamine release in the striatum (Buckholtz et al., 2010). In addition, neuroimaging studies have demonstrated that high impulsivity was associated with gray matter reductions in the orbitofrontal cortex (OFC) (Matsuo et al., 2009) and with increased functional connectivity (FC) within nodes of the striatal-thalamic-cortical circuit (Korponay et al., 2017). Notably, whereas the abovementioned study focused on FC

correlates of individual dimensions of impulsivity, it was focused on a seed-based approach with an emphasis on basal ganglia nuclei.

In this work, we aim to complement these previously reported neurobiological correlates of impulsivity. We aimed to characterize how different dimensions of impulsivity (as measured with the UPPS-P) are associated with brain functional organization. For this purpose, we adapted the UPPS-P to European Portuguese, by assessing the validity evidence of the instrument with a combined implementation of factor analytic procedures. Finally, using a functional magnetic resonance imaging (fMRI) investigation, we assessed the relationship between the variation of each dimension of impulsivity with whole-brain resting-state functional connectivity. With this, we intended to identify networks of brain regions that are associated with the variation of impulsivity traits.

Study I: Psychometric properties of the UPPS-P scale

Methods

The detailed description regarding the pipeline for the adaptation of the UPPS-P for European Portuguese is summarized on the Supplementary Information. A sample of 379 individuals (28.2% males), with an average of 26.52 years (SD=5.93) participated in this study. Only native Portuguese speakers were included in this study.

Measures

The UPPS-P is a self-report instrument comprised of 59 items. For each item, subjects are asked to respond on a scale from 1 (Agree strongly) to 4 (Disagree strongly). Previous reports have provided adequate validity evidence for the instrument. In addition, it has been demonstrated that the factor structure of the UPPS-P is invariant across sex (Cyders, 2013).

The Barratt Impulsiveness Scale-11 (BIS-11, Patton, Stanford, & Barratt, 1995) is a 30-item self-report instrument of impulsivity, which measures three dimensions: motor impulsivity, attention impulsivity, and non-planning impulsivity.

The NEO-FFI-R is a self-reported measure of personality. It assesses five dimensions: neuroticism, extroversion, agreeableness, consciousness and openness to experience. In this work, we used a short version of the instrument, with 20 items, which previously demonstrated adequate psychometric properties for the Portuguese population

The Emotion Regulation Questionnaire (ERQ) assesses the tendency to regulate emotions in two dimensions: cognitive reappraisal and expression suppression (Gross & John, 2003). The instrument is comprised of ten items, presented in a 7-point Likert scale.

Statistical analysis

Evidence based on internal structure of the UPPS-P scale on the Portuguese population was assessed throughout the implementation of complementary strategies, including Confirmatory factor analysis (CFA) and Exploratory Graph Analysis (EGA). The rationale behind this strategy relies on different assumptions: (1) CFA enables a direct comparison between alternative models of relationships among constructs, which is a critical component of theory testing (Strauss & Smith, 2009); (2) nevertheless, the CFA approach typically fails to provide clear support for instruments that apparently had been well established with exploratory factor analysis (EFA) (Marsh et al., 2009).

For the implementation of the network graph analysis, correlations were computed for the 59 items of the UPPS-P. The correlation coefficients were then used for the estimation of a regularized partial correlation network (Epskamp & Fried, 2018). The resulting edge weight parameters were regularized with least absolute shrinkage and selection operator (graphical lasso) to avoid the estimation of spurious (non-meaningful) edges. In the graphical representation of the network, each circle corresponds to a node (an item of the UPPS-P), and each edge is the regularized correlation between two nodes. An edge represents an association between two nodes, after controlling for all other nodes in the network. In statistical terms, a significant edge between two nodes means that the two items of the UPPS-P are strongly connected, such that

when participants score high on one of these items, they are also likely to score high on the other. For confirmatory purposes, different CFA models were implemented: the first (Model 1) specified the five dimensions as correlated latent variables; Model 2 specified second-order latent variables Emotion Based Rash Action (reflected on the first-order latent variables Negative Urgency and Positive Urgency), Sensation Seeking (reflected on a unique first-order latent variable) and Deficits in Conscientiousness (reflected on the first-order latent variables Lack of Premeditation and Lack of Perseverance); Model 3 specified a unique second-order latent variable Impulsivity, which was reflected on each dimension of the UPPS-P.

Reliability of the dimensions comprising the UPPS-P (both long and short versions) was estimated with Cronbach's alpha and MacDonald's omega. The association between UPPS-P and external criteria was performed by means of zero-order correlation analyses.

Statistical analysis was implemented in R (version 3.4.0). CFA was implemented with the *lavaan* package (Rosseel, 2012); EGA was implemented with the *qgraph* (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012), *glasso* (Friedman, Hastie, & Tibshirani, 2014) and *igraph* (Nepusz & Csárdi, 2006). The code and datasets supporting these analyses is available at the Open Science Framework (https://osf.io/bqn79/).

Results

The descriptive statistics for each item are presented on Table S1. The 5-factor solution was supported by three methods: Optimal Coordinates, Parallel Analysis and Velicer MAP. This solution accounted for 58.0% of the total variance of the full instrument. Figure 1 displays the correlograms for the overall scale and for each of the five dimensions.

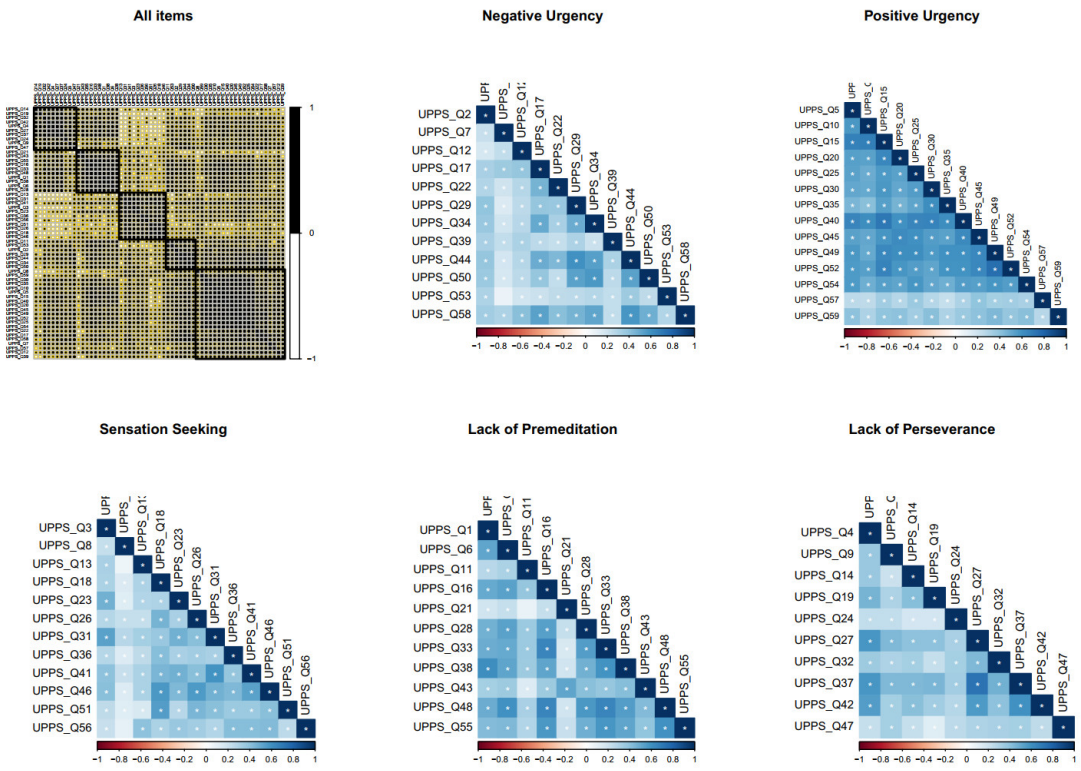

Figure 1. Correlograms between individual variables for the long-version of the scale and for each individual dimension.

The visual representation of the EGA demonstrated that the items belonging to the same theoretical dimension were closer in a two-dimensional space (Figure 2). Regarding the analysis of centrality measures, it was noted that item 58 was the variable with greater levels of closeness and betweenness, whereas item 49 had the greatest strength (Figure S1).

The results from the CFA for Model 1, obtained with three stage robust diagonally least squares estimation, revealed that this factorial solution yielded appropriate fit indices [$\chi^2_{(1642)}$=2677.0, p<.001, CFI=.926, TLI=.923, RMSEA=.046 ($CI_{90\%}$=.043-.049)] (see Supplementary Information for additional details). The different dimensions of the UPPS-P scale demonstrated good internal reliability properties, as demonstrated by Cronbach's alpha and MacDonald's omega coefficients (Table 1). The fit indices for Model 2 (model with three second-order latent variables) were close to Model 1 [$\chi^2_{(1645)}$=2727.9, p<.001, CFI=.925, TLI=.922, RMSEA=.046 ($CI_{90\%}$=.043-.050)]. The unique variable second-order model (Model 3) yielded worse fit indices [$\chi^2_{(1647)}$=2896.7, p<.001, CFI=.914, TLI=.910, RMSEA=.050 ($CI_{90\%}$=.047-.053)].

Table 1. Reliability of the five dimensions of the UPPS-P

	NU	PU	SS	PM	PS
omega_h	0.7130511	0.8797345	0.7133274	0.8226982	0.8133214
Alpha	0.8595192	0.9359935	0.8645789	0.8911962	0.8537704
omega.tot	0.8829171	0.9455707	0.8901655	0.9196543	0.8857279
G6	0.8658683	0.9403602	0.873496	0.8994703	0.8559402

NU – negative urgency; PU – positive urgency; SS – sensation seeking; PM – lack of premeditation; PS – lack of perserverance; omega_h – hierarchical omega (estimate of the general factor saturation); alpha – Cronbach's alpha; omega.tot – amount of variance accounted for by the general factor; G6 – Guttman's Lambda 6 (amount of variance in each item that can be accounted for the linear regression of all of the other items).

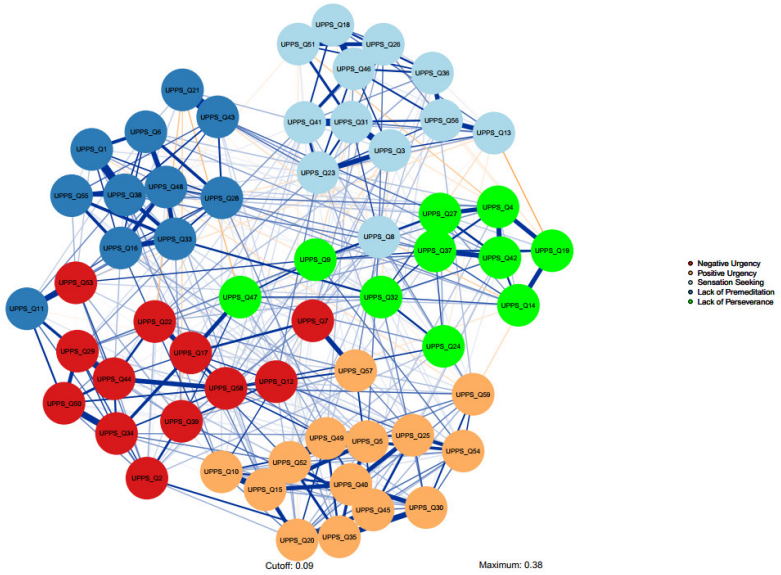

Figure 2. Partial correlation network with LASSO regularization for the long-version of the UPPS-P.

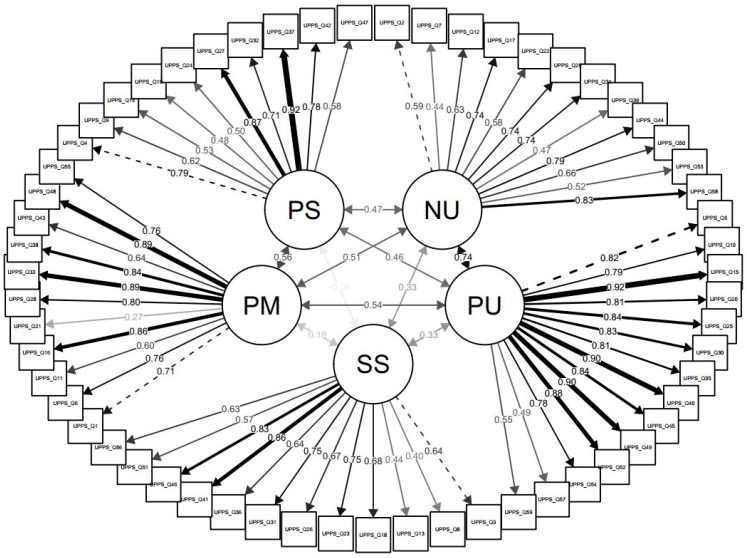

Figure 3. Graphical representation of the confirmatory factor analysis for the long-version of the UPPS-P. Values represent standardized coefficients.

The magnitude of associations between the UPPS-P dimensions was in accordance with previous reports, with a range from r=.084 (between sensation seeking and lack of perseverance) and r=.675 (between negative urgency and positive urgency).

Table 3. Association between dimensions of the UPPS-P and external measures: Barratt Impulsivity Scale (BIS-11), NEO Five-Factor Inventory (NEO-FFI) and Emotion Regulation Questionnaire (ERQ)

Variable	*M*	*SD*	UPPS_NU	UPPS_PU	UPPS_SS	UPPS_PM	UPPS_PS
BIS_AT	16.66	2.85	.17** [.06, .28]	.18** [.07, .28]	.13* [.02, .24]	.25** [.14, .35]	.39** [.29, .48]
BIS_MO	20.26	3.88	.21** [.10, .31]	.30** [.20, .40]	.09 [-.02, .20]	.37** [.27, .46]	.21** [.10, .31]
BIS_NP	22.24	3.98	.19** [.08, .29]	.16** [.05, .27]	.08 [-.03, .19]	.35** [.25, .44]	.22** [.12, .32]
NEO_N	8.54	3.00	.12* [.01, .22]	.09 [-.02, .20]	-.02 [-.13, .09]	-.12* [-.23, -.01]	-.07 [-.18, .04]
NEO_E	9.21	2.58	.13* [.02, .24]	.21** [.10, .31]	.20** [.09, .30]	.12* [.01, .23]	.01 [-.10, .12]
NEO_O	8.42	2.91	.01 [-.10, .12]	.02 [-.09, .13]	.00 [-.11, .11]	-.03 [-.14, .08]	-.02 [-.13, .09]
NEO_A	9.76	3.38	-.13* [-.24, -.02]	-.05 [-.16, .06]	-.07 [-.18, .04]	-.21** [-.32, -.11]	-.30** [-.39, -.19]
NEO_C	11.78	2.16	-.03 [-.14, .08]	.06 [-.05, .17]	.03 [-.08, .14]	-.04 [-.15, .07]	-.22** [-.32, -.11]
ERQ_CR	27.62	6.86	-.04 [-.15, .07]	.01 [-.10, .12]	-.05 [-.16, .06]	-.08 [-.19, .03]	-.11* [-.22, -.00]
ERQ_ES	15.83	5.09	.03 [-.08, .14]	.09 [-.02, .20]	.11* [.00, .22]	-.07 [-.18, .04]	.12* [.01, .23]

M and *SD* are used to represent mean and standard deviation, respectively. Values in square brackets indicate the 95% confidence interval for each correlation. The confidence interval is a plausible range of population correlations that could have caused the sample correlation (Cumming, 2014). * indicates $p < .05$. ** indicates $p < .01$.

Table 3 summarizes the association between UPPS-P dimensions and other external variables. There were low to medium associations between UPPS-P and BIS-11 dimensions, where the correlation coefficients ranged from .083 (sensation seeking with non-planning impulsivity) to .386 (lack of perseverance with attentional impulsivity). Regarding the associations with personality traits, it was observed that the correlation coefficients ranged from r=-.297 (between positive urgency and lack of perseverance) and r=.209 (between positive urgency and extroversion). Finally, the association between the UPPS-P and ERQ had small magnitude for all the pairwise correlations: from r=-.113 (lack of perseverance with cognitive reappraisal) to r=.124 (lack of perseverance with emotional suppression).

Study II: The association between impulsivity and resting-state functional connectivity

Methods

Participants

Fifty-five participants were recruited to perform a multimodal magnetic resonance imaging (MRI) session, comprised of structural and resting-state functional acquisitions.

MRI data acquisition

The imaging sessions were performed on a clinically approved Magnetom Verio 3 T (Siemens, Erlangen, Germany) MRI scanner at the Hospital of Braga, using a Siemens 32-channel receive only head coil. A 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE) structural scan was acquired with the following parameters: repetition time (TR) = 2.42 s, echo time (TE) = 4.13 ms, flip angle (FA) = 9°, 176 sagittal slices, in plane resolution = 1.0 x 1.0 mm2 and slice thickness = 1.0 mm. A multiband echo planar imaging acquisition sensitive to blood-oxygen-level dependent (BOLD) signal was acquired during resting-state, using

the following parameters: TR = 1.19 s, TE = 34 ms, FA = 62°, isometric voxel resolution of 2 mm^3, 72 slices, multi band acceleration factor of 6 and 370 volumes (Feinberg et al., 2010; Moeller et al., 2010; Xu et al., 2013). During the resting-state acquisition, participants were instructed to remain still, awake, with their eyes closed, as motionless as possible and to try to think of nothing in particular. A certified neuroradiologist visually inspected all images to confirm that they were not affected by critical motion and that participants had no brain lesions or pathology. One participant was excluded due to unsuitable data quality.

Resting-state fMRI data preprocessing was implemented with FMRIB Software Library (FSL v5.07; http://fsl.fmrib.ox.ac.uk/fsl/) tools, comprising the following steps: slice timing correction, inputting a costume file describing the timings of each slice; head motion correction using the mean functional image as the reference, followed by motion scrubbing to reduce potential contamination of motion outliers on functional connectivity (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012). Another subject was here excluded due to excessive motion (exceeding the voxel size) (Soares et al., 2016). To further remove typical confounding signals linear regression of motion parameters, mean WM and cerebrospinal fluid (CSF) signal and motion outliers was performed. Functional images were spatially normalized to the Montreal Neurological Institute (MNI) standard space through a procedure that included the following steps: (i) skull stripping of the mean image of the functional acquisition and of the structural acquisition; (ii) rigid-body registration of the skull-stripped mean functional image to the skull stripped structural scan; (iii) affine registration of the structural scan to the MNI T1 template; (iv) nonlinear registration of the structural scan to the MNI T1 template using the affine transformation previously estimated as the initial alignment; (v) nonlinear transformation of the functional acquisition to MNI standard space trough the sequential concatenation and application of the rigid-body transformation. The residual images were then spatially smoothed with a Gaussian kernel of 3 mm full-width at half maximum and band-pass temporal filtered (0.01-0.08Hz).

Resting-state FC analysis

Whole-brain functional connectomes were built by extracting the mean time-series of the 116 regions of the Automatic Anatomical Labeling (AAL) atlas. A symmetric adjacency matrix R

was then produced, where each cell r_{ij} corresponded to the correlation coefficient (r) between the time-series of each region. This matrix was transformed with Fisher's r-to-Z transformation to convert Pearson r coefficients to normally distributed Z-values. The group matrix was used as the input for the network-based statistic (NBS) procedure (Zalesky, Fornito, & Bullmore, 2010), which implements statistical testing in two consecutive phases: initially the hypothesis is tested in each network edge and a user-defined significance threshold applied to filter surviving connections; second, sub-networks composed of connections whose significance surpasses the threshold are identified and determining its significance according to the network size. The significance of the obtained sub-networks was estimated by comparing their sizes with the distribution of the size of sub-networks obtained through 5000 random permutations of the original hypothesis, using three complementary significance thresholds (α=.0001, α=.0005 and α=.001). BrainNet Viewer (http://www.nitrc.org/projects/bnv) (Xia, Wang, & He, 2013) was used to display significant networks. Graph-theory analysis was used to assess the impact of impulsivity dimensions on three typical local network metrics, allowing to gain a better understanding of the dynamic organization of individual nodes.

The Brain Connectivity Toolbox (Rubinov & Sporns, 2010) was used for the estimation of node-level graph metrics, including (1) local clustering coefficient, a measure of segregation determined by number of edges between the nearest neighbors of a node in proportion to the maximum number of possible edges (2) local efficiency, another segregation measure representing the average inverse shortest path length on the neighborhood of the node and (3) nodal degree, a centrality measure, which reflects the tendency of a node to interact with others, and is calculated as the number of all of its connections (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010). These metrics were calculated along a range of densities from 0.1 to 0.45 in steps of 0.025. The statistical testing consisted of fitting a General Linear Model for each metric at each density step. To detect the most significant results we searched for metrics/nodes combinations surviving different significance thresholds at different network densities. We focused on results consistently surviving correction for the number of areas tested (α =.05/116) and for the number of areas and number of variable of interests (α=.05/(116*5)) across several thresholds.

The model used for both NBS testing and for testing the network metrics included the five sub-dimensions of the impulsivity scale (NU, PU, SS, PM and PS), while controlling for gender and age.

Results

Using the most conservative significance threshold ($t_{(45)}$=4.26, corresponding to a significance level of p=.0001) we did not detect any significant finding. With an edge threshold with a significance of p=.0005 ($t_{(45)}$=3.75), there was a significant, positive association, between the lack of premeditation dimension and a network with a pseudo-bilateralized configuration, comprised of nodes on the putamen (left and right), amygdala (left and right) and the cerebellum (Figure 5). No other significant association was obtained for the remaining impulsivity dimensions, using this statistical threshold. Using a more liberal threshold of statistical significance ($t_{(45)}$=3.52, corresponding to a two-tailed significance of p=.001), we observed that negative urgency displayed a negative association with a network comprised of nodes such as the bilateral temporal superior, bilateral Heschl, supplementary motor area, middle cingulum and cerebellum of the left hemisphere, insula and supramarginal, from the right hemisphere (Figure 6).

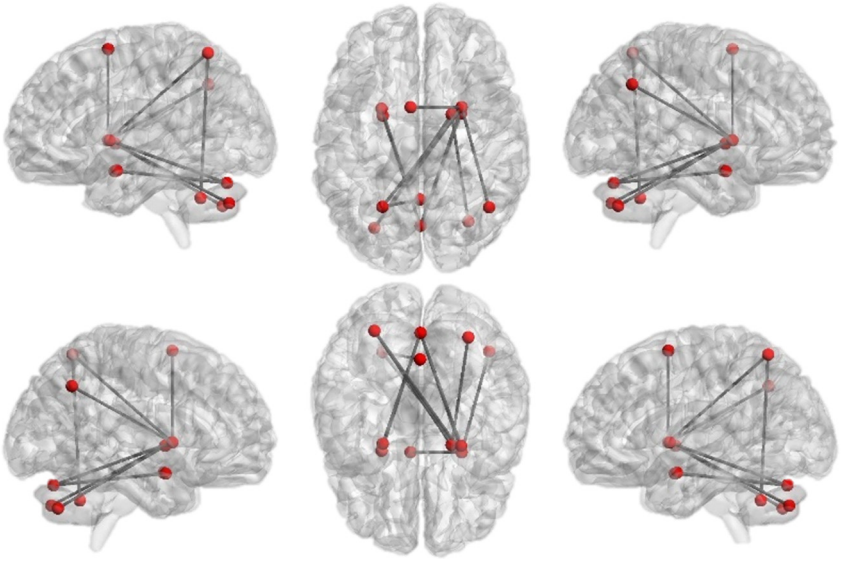

Figure 5. Results of network-based statistics. Lack of Premeditation has a statistically significant association with a network comprised of bilateral putamen, bilateral amygdala and cerebellum.

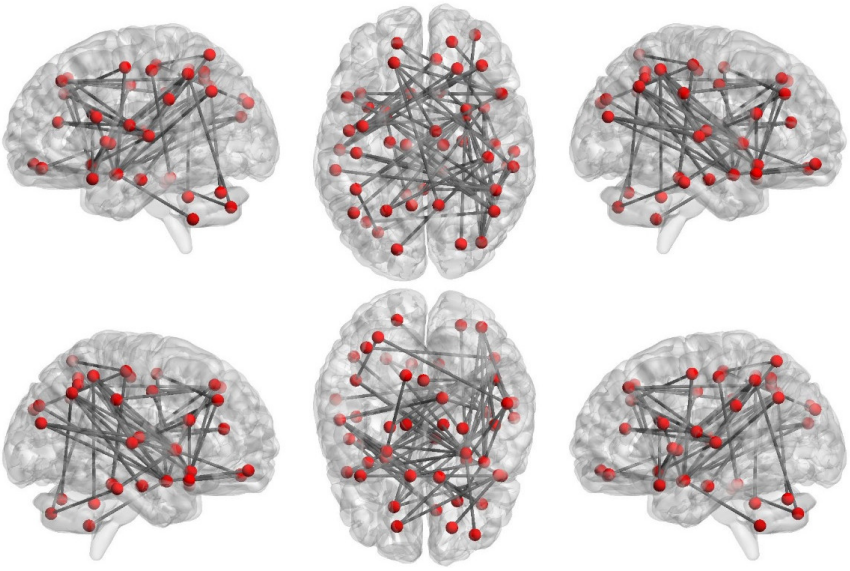

Figure 6. Results of network-based statistics. Negative Urgency has a statistically significant negative association with a network comprised of cingular regions, bilateral insula, cerebellum and Heschl gyri.

On the network metrics strong significant associations were found between NU and the nodal degrees of nodes 82-Temporal Superior Right (with significance in eight densities surviving the highest threshold – from densities of 0.1 to 0.15 and from 0.35 to 0.45 - and four others surviving the second threshold – densities of 0.175, 0.2, 0.3 and at 0.325) and 81-Temporal Superior Left (with significance in 4 densities surviving the secondary threshold – from densities of 0.2 to 0.25 and at 0.35 -, while several fell just short). These significances are plotted in Figure 7 where points surviving the highest threshold are plotted in red, surviving the secondary threshold in blue and all others in black. In both situations the associations were negative, meaning that an increase in NU led to a decrease in the nodal degree. No other extended associations were found, although associations for a single density level surviving the secondary threshold were found for: the cluster degree of node 37 – Left Hippocampus with a positive association with PU, $p=2.5x10^{-4}$, for a density of 0.125; and the cluster degree of node 65 – Left Angular with a positive association with PM, a $p=1.5x10^{-4}$, for a density of 0.225.

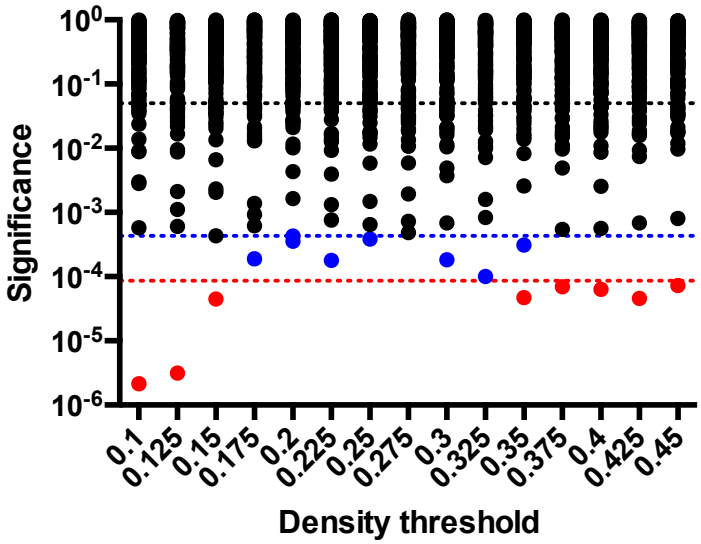

Figure 7. Scatter plot of the significance of the association between the nodal degree and NU for all 116 nodes through the 15 density thresholds. Horizontal lines mark the significances of α=0.05 in black, α=0.05/116 in blue and α=0.05/(116*5) in red. Points surviving the two higher thresholds are color coded in the appropriate color. Y-axis represented in logarithmic base 10 scale.

Discussion

In this work, we adapted and tested the psychometric properties of the UPPS-P in a convenience Portuguese sample. Using a complementary approach of exploratory and confirmatory factor analytic strategies, we provided support for the demonstration of validity evidence for the instrument. In addition, we extended the psychometric characterization of the scale to the neurobiological level, where we searched for neuroimaging correlates of different dimensions of the scale. With this approach, we could demonstrate that specific dimensions of impulsive behavior are characterized by neurobiological correlates. Two dimensions of the UPPS-P, negative urgency and lack of premeditation, were significantly associated with resting-state functional connectivity at the whole-brain level, when controlling for the variation of the remaining impulsivity dimensions. Specifically, we found that negative urgency was associated with the functional connectivity of a network comprised of insula, cerebellum, sensorial and temporal nodes. On the other hand, lack of premeditation was strongly associated with a network comprised of basal ganglia nuclei, amygdala and cerebellum. Finally, negative urgency was found to be significantly associated with reduced node degree of bilateral superior temporal

regions, whereas positive urgency had significant, positive associations with node degree of the left hippocampus and left angular gyrus.

The dependence of impulsivity on the function of cortico-striatal loops has been progressively established among the neuroscience literature (Dalley et al., 2011). These results corroborate a previously reported association between impulsivity traits and basal ganglia FC, obtained with a seed-based analysis (Korponay et al., 2017). In addition, FC between basal ganglia nuclei and OFC nodes was previously associated with impulsivity-related personality characteristics (Angelides, Gupta, & Vickery, 2017). As previously hypothesized, this altered connectivity of basal ganglia nuclei may be linked with an increased difficulty of highly impulsive individuals to inhibit the urge to act (Korponay et al., 2017). Nonetheless, we also observed that this network is also comprised limbic nodes – which highlights a likely involvement of affect-related processing underlying the manifestation of this dimension of impulsivity. Previous evidence has demonstrated an association between impulsivity trait and resting-state FC between the amygdala and the anterior cingulate cortex (Kerr et al., 2014). These findings seem to support the relevance of the amygdala on the processing of emotionally-relevant stimuli in the context of reward processing (Peck, Lau, & Salzman, 2013).

We also noted that one of the dimensions related with urgency – negative urgency – has a strong negative impact on the FC of a widespread network. To the best of our knowledge, the description of the neurobiological correlates of affect-related dimensions of impulsivity has not been previously reported in the literature. This highlights the fact that affective drivers of impulsive behavior may have a relevant neurobiological meaning, being associated with a complex network of FC characterized by the involvement of several lobes, from both hemispheres, including the insula, anterior and middle cingulum, supplementary motor area, postcentral and of distinct cerebellar nodes. These results also highlight the involvement of the cerebellum on non-motor related functions, corroborating previously reported descriptions of the role of the cerebellum in cognition, emotion and decision-making processing (Schmahmann, 2010).

The interpretation of these findings should consider some limitations. First, the UPPS-P was administered to a convenience sample, which was mainly constituted by young adults with high education levels. While this strategy has been used in previous validations of the instrument,

it would be interesting to assess how distinct impulsivity dimensions are associated with neurobiological patterns in other populations.

This study focused on patterns of brain FC in the absent of an active task. Even though one may argue that resting-state FC may constitute a more valid means of assessing the default functional organization of the brain as a network (as it is independent of an external stimulation), we cannot exclude the possibility that specific patterns of FC may emerge during task-performance, particularly with impulsivity-related stimuli. Furthermore, the current approach does not allow the establishment of causality, *i.e.*, whether the disturbance of a specific node implicates the response of another node. As such, future studies may implement complementary evidence to this work, by assessing the patterns of interaction between distinct brain nodes during impulsivity tasks with methodologies such as psychophysiological interactions or dynamic causal modelling. In addition, future studies may address the neurobiological correlates of impulsivity dimensions across a wider age range.

In sum, this work provides additional validity evidence of UPPS-P. To the best of our knowledge, this work constitutes a unique report of a combined description of the whole-brain connectome and graph-theory metrics at the local level, which allowed us to demonstrate that distinct facets of impulsivity are characterized by different patterns of resting-state functional connectivity. Altogether, these findings provide a neurobiological support for the multifaceted nature of this trait.

Acknowledgements

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Supplementary Information

Adaptation of the UPPS-P for European Portuguese

Two independent researchers (PSM and LNS) conducted individual translations of the instrument. Next, two other researchers compared the two independent translations, focusing on semantic (PC) and conceptual similarities (PRA) between the translated and the original versions. After the evaluation of each individual item, a version of the instrument was submitted to back-translation by an independent bilingual researcher (MS) without prior contact with the original version of the manuscript. The resulting back-translated version was then compared with the original version of the UPPS-P. This last phase was performed by a native English speaker (EG), which highlighted whether adjustments were needed with the goal of maintaining the meaning of each individual item. For the back-translated items with large semantic or conceptual differences from the original version, new translations were proposed with the goal of maximizing the similarities between versions. After consensual agreement, the final back-translated version was sent to the authors of the original version for validation.

In this work, we examined the psychometric characteristics of the full version of the manuscript (comprised of 59 items), together with a reduced version with 20 items, which has been widely used in different countries. For both versions, we assessed the descriptive statistics for individual items and their factor structure, using a combined implementation of exploratory and confirmatory factor analysis. For the former, we implemented an exploratory graph analysis; for the second, a diagonal weighted least squares estimation was performed, to account for the ordinal nature of the items.

Descriptive Statistics

The descriptive statistics for the long and short versions of the UPPS-P are presented on Table S1 and Table S2, respectively.

Table S1. Descriptive statistics for each individual item of the UPPS-P

Item	Mean	SD	SE	Median	Trimmed Mean	Min	Max	Sk	K
UPPS_Q1	1.72	0.65	0.04	2	1.66	1	4	0.71	1.01
UPPS_Q2	2.09	0.78	0.04	2	2.06	1	4	0.38	-0.22
UPPS_Q3	2.76	0.75	0.04	3	2.76	1	4	-0.14	-0.37
UPPS_Q4	1.44	0.64	0.04	1	1.35	1	4	1.43	2.08
UPPS_Q5	1.62	0.77	0.04	1	1.48	1	4	1.2	1.07
UPPS_Q6	1.53	0.65	0.04	1	1.45	1	4	1.1	1.3
UPPS_Q7	2.17	0.98	0.06	2	2.09	1	4	0.29	-1.02
UPPS_Q8	2.31	0.99	0.06	2	2.27	1	4	0.1	-1.1
UPPS_Q9	1.71	0.75	0.04	2	1.61	1	4	0.85	0.27
UPPS_Q10	1.54	0.69	0.04	1	1.43	1	4	1.18	1.17
UPPS_Q11	2.19	0.85	0.05	2	2.16	1	4	0.21	-0.66
UPPS_Q12	2.18	0.79	0.05	2	2.16	1	4	0.28	-0.34
UPPS_Q13	2.52	0.97	0.06	3	2.52	1	4	0	-0.98
UPPS_Q14	1.8	0.79	0.05	2	1.72	1	4	0.72	-0.06
UPPS_Q15	1.44	0.65	0.04	1	1.35	1	4	1.51	2.5
UPPS_Q16	1.66	0.66	0.04	2	1.58	1	4	0.77	0.65
UPPS_Q17	1.81	0.86	0.05	2	1.71	1	4	0.77	-0.29
UPPS_Q18	2.61	1.15	0.07	3	2.64	1	4	-0.18	-1.41
UPPS_Q19	1.97	0.69	0.04	2	1.94	1	4	0.39	0.15
UPPS_Q20	1.48	0.69	0.04	1	1.35	1	4	1.4	1.61
UPPS_Q21	2.06	0.78	0.04	2	2.02	1	4	0.4	-0.24
UPPS_Q22	2.02	0.89	0.05	2	1.95	1	4	0.51	-0.57
UPPS_Q23	2.05	0.86	0.05	2	2.02	1	4	0.25	-0.92
UPPS_Q24	2.2	0.78	0.04	2	2.18	1	4	0.36	-0.18
UPPS_Q25	1.56	0.74	0.04	1	1.43	1	4	1.19	0.83
UPPS_Q26	2.74	1.18	0.07	3	2.79	1	4	-0.35	-1.38
UPPS_Q27	1.71	0.7	0.04	2	1.61	1	4	0.87	0.98
UPPS_Q28	1.58	0.62	0.04	2	1.52	1	4	0.83	0.83
UPPS_Q29	2.1	0.82	0.05	2	2.08	1	4	0.23	-0.69
UPPS_Q30	1.35	0.64	0.04	1	1.23	1	4	1.96	3.92
UPPS_Q31	2.66	0.86	0.05	3	2.7	1	4	-0.25	-0.56
UPPS_Q32	1.74	0.76	0.04	2	1.63	1	4	0.96	0.8
UPPS_Q33	1.66	0.65	0.04	2	1.6	1	4	0.83	1.2
UPPS_Q34	2.08	0.87	0.05	2	2.02	1	4	0.41	-0.59
UPPS_Q35	1.35	0.63	0.04	1	1.23	1	4	1.8	2.93
UPPS_Q36	2.28	1.17	0.07	2	2.22	1	4	0.26	-1.43
UPPS_Q37	1.7	0.69	0.04	2	1.61	1	4	0.83	0.77
UPPS_Q38	1.64	0.64	0.04	2	1.57	1	4	0.72	0.53
UPPS_Q39	2.49	0.82	0.05	2	2.48	1	4	0.02	-0.55
UPPS_Q40	1.41	0.65	0.04	1	1.29	1	4	1.61	2.38
UPPS_Q41	2.2	0.94	0.05	2	2.16	1	4	0.1	-1.12
UPPS_Q42	1.65	0.74	0.04	2	1.53	1	4	1.14	1.35
UPPS_Q43	1.56	0.61	0.03	2	1.51	1	4	0.85	1
UPPS_Q44	1.98	0.89	0.05	2	1.91	1	4	0.46	-0.74
UPPS_Q45	1.64	0.76	0.04	1	1.53	1	4	1	0.41
UPPS_Q46	2.13	1.12	0.06	2	2.04	1	4	0.42	-1.27
UPPS_Q47	2.02	0.84	0.05	2	1.96	1	4	0.51	-0.34
UPPS_Q48	1.64	0.65	0.04	2	1.57	1	4	0.8	0.76
UPPS_Q49	1.56	0.72	0.04	1	1.43	1	4	1.19	1.02
UPPS_Q50	2.39	0.89	0.05	2	2.37	1	4	0.04	-0.78
UPPS_Q51	3.04	1.07	0.06	3	3.17	1	4	-0.78	-0.71
UPPS_Q52	1.65	0.75	0.04	2	1.54	1	4	0.95	0.36
UPPS_Q53	2.4	0.7	0.04	2	2.41	1	4	0.15	-0.19
UPPS_Q54	1.67	0.81	0.05	1	1.55	1	4	0.97	0.06
UPPS_Q55	1.74	0.66	0.04	2	1.67	1	4	0.54	0.12
UPPS_Q56	2.56	1.17	0.07	3	2.58	1	4	-0.09	-1.47
UPPS_Q57	2.13	0.91	0.05	2	2.07	1	4	0.36	-0.76
UPPS_Q58	2.24	0.85	0.05	2	2.23	1	4	0.06	-0.81
UPPS_Q59	2.11	0.91	0.05	2	2.05	1	4	0.3	-0.88

SD – Standard Deviation; SE – Standard Error; Sk – Skewness; K – Kurtosis; Min – Minimum; Max - Maximum.

Table S2. Descriptive statistics for each individual item of the UPPS-P

Item	Mean	SD	SE	Median	Trimmed Mean	Min	Max	Sk	K
UPPS_Q01	1.81	0.86	2	1.71	1	4	0.77	-0.29	0.05
UPPS_Q02	2.02	0.89	2	1.95	1	4	0.51	-0.57	0.05
UPPS_Q03	2.1	0.82	2	2.08	1	4	0.23	-0.69	0.05
UPPS_Q04	2.08	0.87	2	2.02	1	4	0.41	-0.59	0.05
UPPS_Q05	1.44	0.64	1	1.35	1	4	1.43	2.08	0.04
UPPS_Q06	1.8	0.79	2	1.72	1	4	0.72	-0.06	0.05
UPPS_Q07	1.97	0.69	2	1.94	1	4	0.39	0.15	0.04
UPPS_Q08	1.71	0.7	2	1.61	1	4	0.87	0.98	0.04
UPPS_Q09	1.53	0.65	1	1.45	1	4	1.1	1.3	0.04
UPPS_Q10	1.66	0.66	2	1.58	1	4	0.77	0.65	0.04
UPPS_Q11	1.58	0.62	2	1.52	1	4	0.83	0.83	0.04
UPPS_Q12	1.64	0.65	2	1.57	1	4	0.8	0.76	0.04
UPPS_Q13	2.05	0.86	2	2.02	1	4	0.25	-0.92	0.05
UPPS_Q14	2.66	0.86	3	2.7	1	4	-0.25	-0.56	0.05
UPPS_Q15	2.28	1.17	2	2.22	1	4	0.26	-1.43	0.07
UPPS_Q16	2.13	1.12	2	2.04	1	4	0.42	-1.27	0.06
UPPS_Q17	1.54	0.69	1	1.43	1	4	1.18	1.17	0.04
UPPS_Q18	1.48	0.69	1	1.35	1	4	1.4	1.61	0.04
UPPS_Q19	1.35	0.63	1	1.23	1	4	1.8	2.93	0.04
UPPS_Q20	1.65	0.75	2	1.54	1	4	0.95	0.36	0.04

SD – Standard Deviation; SE – Standard Error; Sk – Skewness; K – Kurtosis; Min – Minimum; Max - Maximum.

Psychometric characteristics of the short and long versions of the UPPS-P

The factor loadings ranged from .451 (item 7) to .824 (item 58) for the negative urgency dimension; from .481 (item 57) to .917 (item 15) for the positive urgency dimension; from .412 (item 8) to .872 (item 41) for sensation seeking; from .280 (item 21) to .889 (item 48) for lack of premeditation; from .480 (item 19) to .920 (item 37) for lack of perseverance (Figure 3). A sensitivity analysis was conducted to assess the impact of the lowest loading (*i.e.,* item 21) on the overall fit indices. We noted slight improvements on model fit indices [$\chi^2_{(1585)}$=2548.1, p<.001, CFI=.931, TLI=.928, RMSEA=.045 ($CI_{90\%}$=.042-.048)]. Nevertheless, to maintain the comparability of this translation with other versions of the manuscript, we decided to keep the original structure without the deletion of this item.

In contrast with the long version of the manuscript, the results from the parallel analysis provide support for a 4-factor structure of the short version of the UPPS-P. In fact, this factorial structure was supported by four additional methods for determining the number of factors to retain, including Optimal Coordinates, Velicer MAP, BIC and VSS Complexity 2. On the other hand, the 5-factor structure was supported by only one method.

The results from the CFA, obtained with three stage robust diagonally least squares estimation, revealed that this factorial solution yielded appropriate fit indices [$\chi^2_{(1642)}$=2677.0, p<.001, CFI=.926, TLI=.923, RMSEA=.046 ($CI_{90\%}$=.043-.049)]. The factor loadings ranged from .451 (item 7) to .824 (item 58) for the negative urgency dimension; from .481 (item 57) to .917 (item 15) for the positive urgency dimension; from .412 (item 8) to .872 (item 41) for sensation seeking; from .280 (item 21) to .889 (item 48) for lack of premeditation; from .480 (item 19) to .920 (item 37) for lack of perseverance.

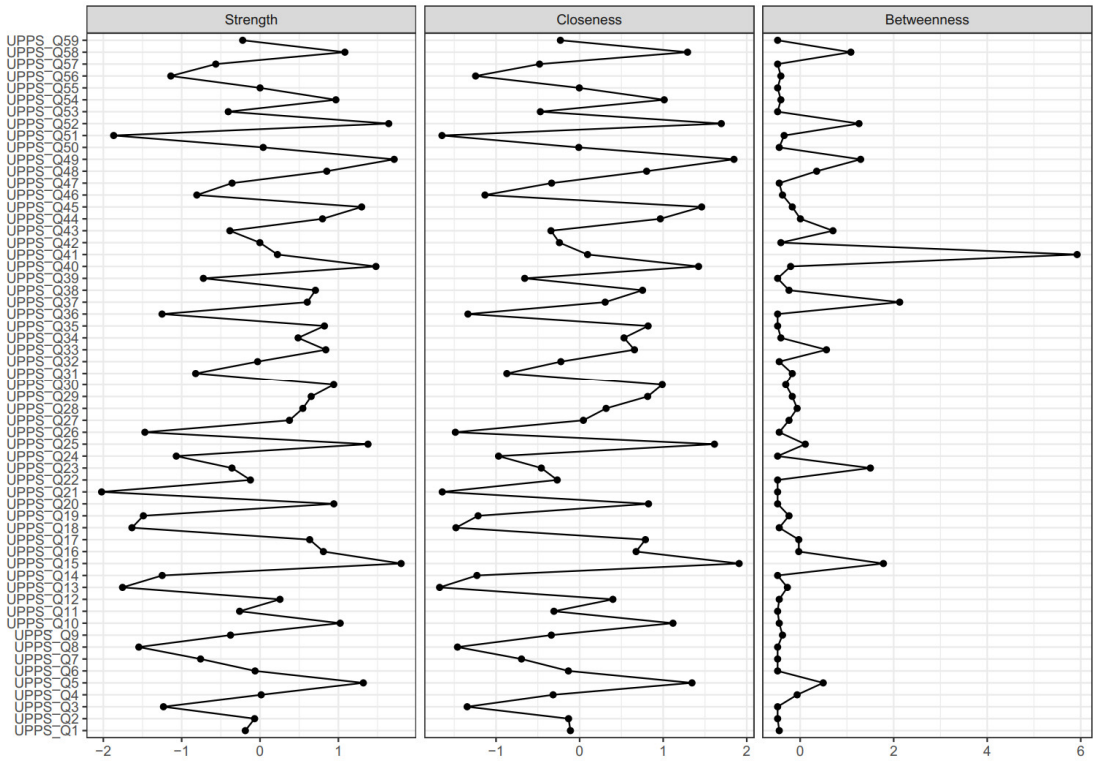

Figure S1. Results of the centrality analysis represent three centrality measures: node strength, closeness and betweenness.

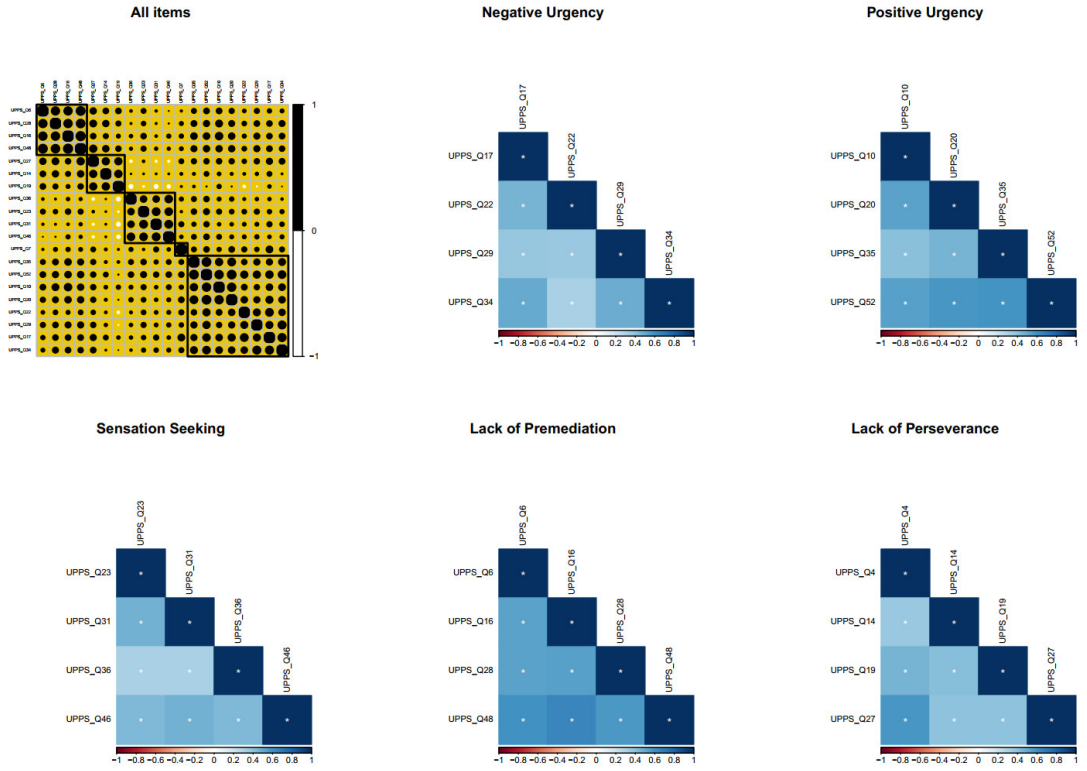

Figure S2. Correlograms between individual variables for the short-version of the scale and for each individual dimension.

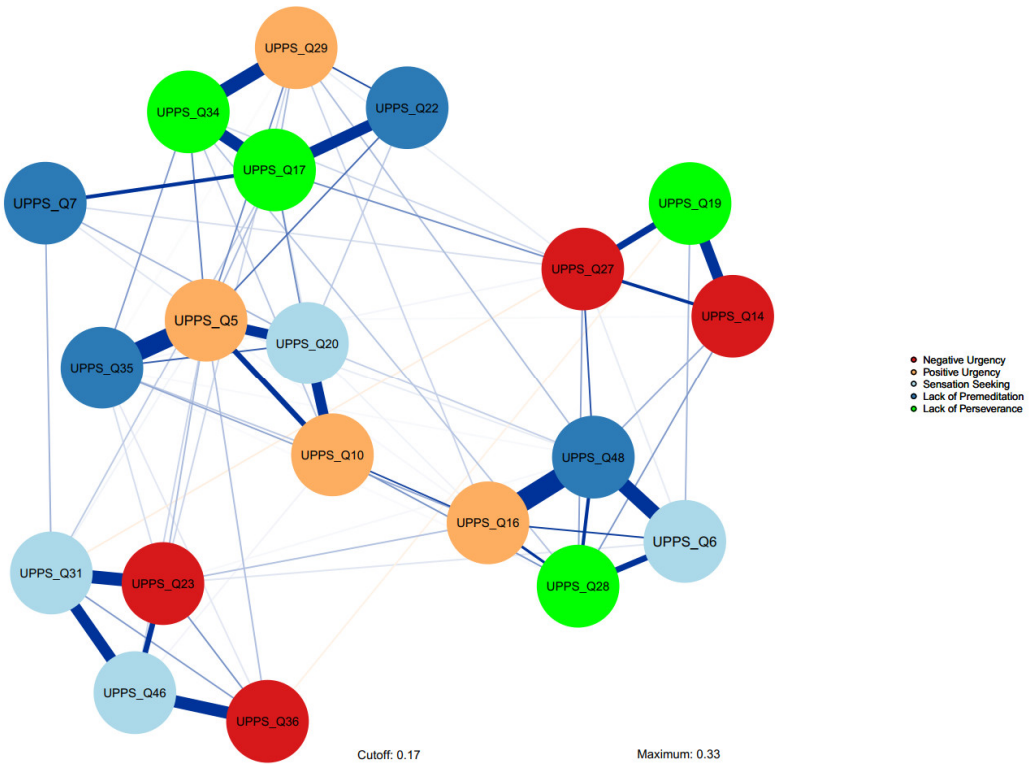

Figure S3. Partial correlation network with LASSO regularization for the short-version of the UPPS-P.

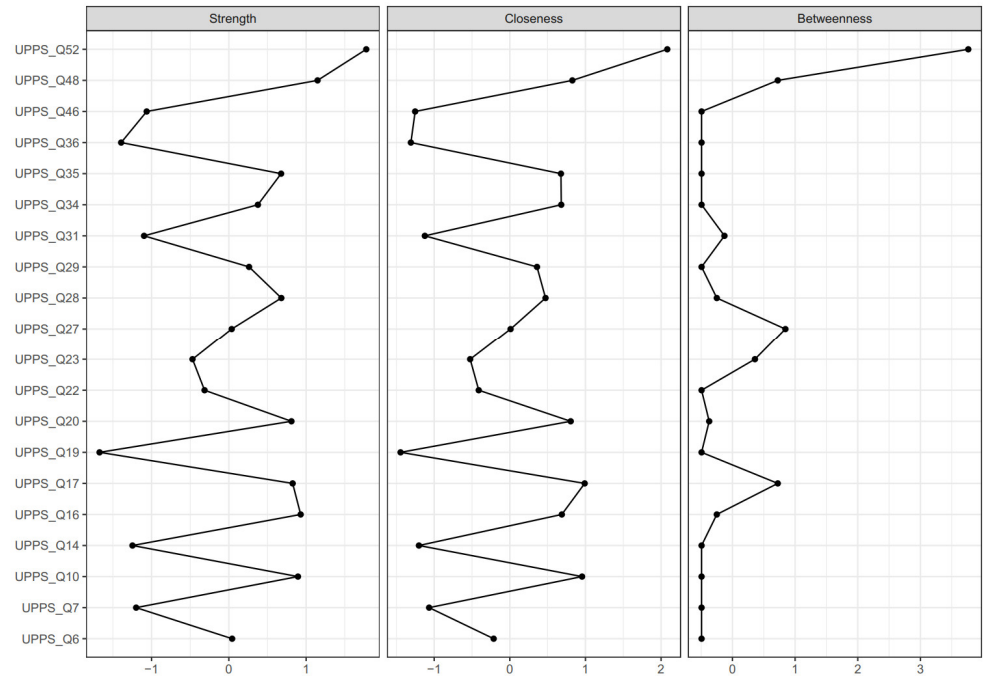

Figure S4. Results of the centrality analysis represent three centrality measures (node strength, closeness and betweenness) for the short-version of the UPPS-P.

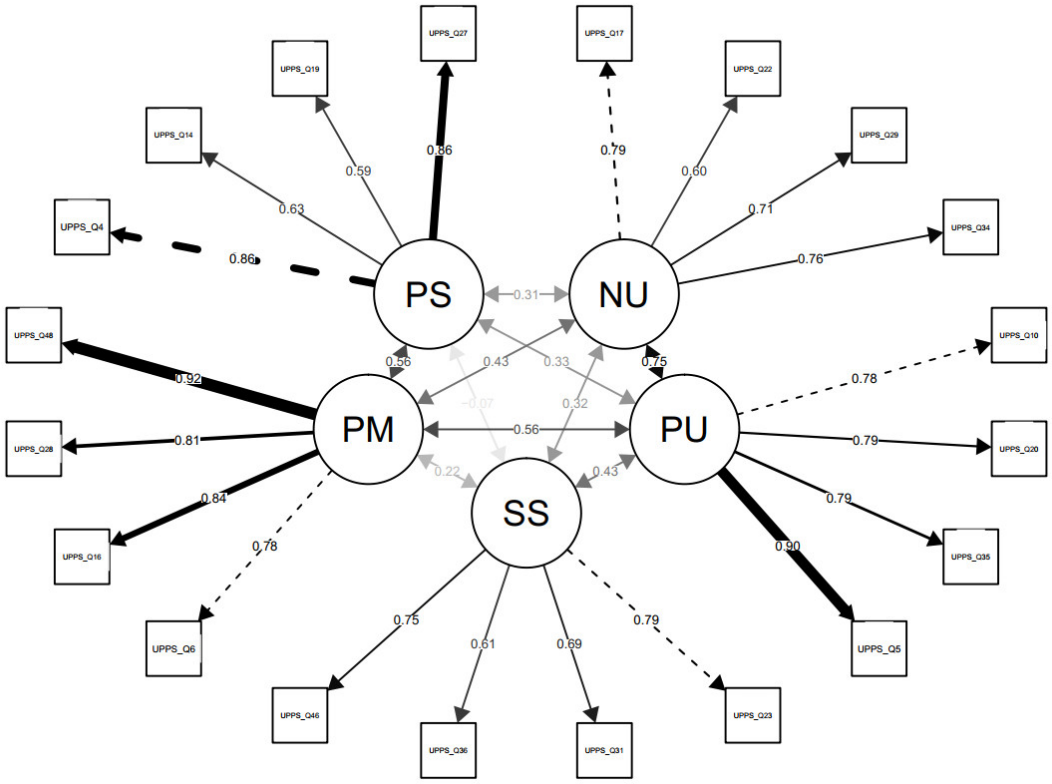

Figure S5. Graphical representation of the confirmatory factor analysis for the short-version of the UPPS-P. Values represent standardized coefficients.

CHAPTER 4.2

Acting on my feelings: emotional interference during decision-making

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In Preparation

Acting on my feelings: emotional interference during decision-making

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Abstract

There is a large variety of context-related aspects that shape our decisions. One such aspect is related with the emotional state. Previous studies have suggested that emotional arousal has a role on the modulation of risk-taking behavior in gambling tasks. In this study, we aimed to test this hypothesis. For this purpose, we developed an experimental apparatus, in which we presented highly arousing stimuli with opposing hedonic valences (either positive or negative stimuli) as a strategy for inducting an emotional state. Under such experimental contingencies, individuals performed a risky decision-making task – the Balloon Analogue Risk Task (BART) – in which they accumulate gains each time they decide to inflate a balloon; however, participants lose the accumulated money if the balloon explodes. Of note, the threshold for explosion is randomly defined and thus it is unknown for the participant – as such, each time an individual inflates the balloon, participants engage in a gambling behavior. In contrast with theoretical conceptualizations pertaining to the role of arousal on risky decision-making, only stimuli with positive hedonic valence influenced risk-taking – individuals in this experimental condition displayed a reduced tendency to gamble. On the other hand, subjects exposed to the negative emotional induction did not show an altered risky decision-making profile. These results highlight the need for further studies examining the nature of the association between induced emotional experience and risk-taking.

Background

Traditional accounts in the field of decision theory have focused on the role of cognition and situational processes on human decision-making (Lerner, Li, Valdesolo, & Kassam, 2015). On the other hand, the role of emotion on these processes was for a long time neglected in the field of economics. The findings from neuroscience studies have highlighted the relevance of emotions as important modulators of decision-making (Camerer, Loewenstein, & Prelec, 2005; Loewenstein, Weber, Hsee, & Welch, 2001). Lesion studies, for instance, demonstrated that damages in the ventromedial prefrontal cortex (vmPFC) are related with an inability to feel emotions and to make optimal decisions (Bechara, Damasio, Damasio, & Lee, 1999) (Damasio, 1994)). Currently, emotion is considered in economic models of individual choice ((Bernheim & Rangel, 2004) (Caplin & Leahy, 2001)). However, the mechanisms by which emotion impacts on decision-making are not well understood. One hypothesis that has gained general acceptance among the scientific literature relies on the role of arousal on the patterns of risk-seeking and risk-aversion (Lo & Repin, 2002). Within this perspective, positive arousal associated with anticipation of gain is expected to promote risk taking; on the other hand, negative arousal associated with anticipation of loss is expected to promote risk aversion (Kuhnen & Knutson, 2005) (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003).

The induction of emotional states is a typical experimental approach to investigate how emotion influences a panoply of neurobehavioral processes (Westermann, Spies, Stahl, & Hesse, 1996). Distinct modalities have been used to induce emotional states, including the presentation of static pictures (Lang & Bradley, 2007), recall of past events (Chanel, Kierkels, Soleymani, & Pun, 2009), films (Gross & Levenson, 1995), music (Baumgartner, Esslen, & Jäncke, 2006) or olfactory stimuli (Royet et al., 2000). This approach is typically successful on the modulation of several neurobiological responses, including central responses observed in functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) studies, as well as peripheral responses from the autonomic nervous system, involving the facial, cardiac, respiratory and the electrodermal systems. In this study, we aimed to investigate the impact of the induction of contrasting affective states on decision-making behavior.

The current work

In this work, we examined the role of the induction of an emotional state on patterns of risky decision-making. Following the findings from previous studies, we hypothesized that the induction of positive and, particularly, negative emotional induction would be associated with an altered risk-taking behavior. For this purpose, we implemented an experimental paradigm with the aim of understanding whether a prolonged audiovisual form of emotional induction would lead to pronounced behavioral differences in decision-making profiles.

Methods

Participants

A sample of 92 healthy individuals (62.9% females; mean age=29.9 (SD=8.67)) recruited at the University of Minho (Braga, Portugal) participated in this study. All participants were Portuguese-speaking citizens. None of the participants reported any history of neurologic or psychiatric conditions. The experimental procedures were approved by the local Institutional Review Board. Before the experiment, written informed consent was obtained from each point and the goals of the experiment were carefully explained. In addition, participants were informed about the voluntary nature of their participation. They were instructed that they would be able to withdraw from the experiment at any point and at no cost. During the presentation of the experimental apparatus, participants were told that their data would remain confidential.

The experiment was performed in a sound-attenuated room, where the participants were comfortably seated. The experimental stimuli were presented in on a 15.6" full-HD laptop at a viewing distance of 55 cm under low light. PsychoPy v3.0 was used for displaying the experimental stimuli. The code for the experimental apparatus is available at the Open Science Framework (OSF; https://osf.io/4cjmy/).

Emotion induction strategy

Participants were pseudo-randomly assigned to one of three groups: positive stimulation (PS), control stimulation (CS) and negative stimulation (NS). Each group was involved in a sequential experimental apparatus, comprised of a 60s baseline acquisition, video visualization and auditory stimulation concurrently with a risky decision-making task. The experimental apparatus is represented on Figure 1. The strategy of combining videos and music is aimed to produce a more sustained emotional induction. The video stimuli were selected from the FilmStim database (Schaefer, Nils, Sanchez, & Philippot, 2010). For the PS condition, a fragment from the film "Life is Beautiful" was selected. This clip describes a father and a boy talking to a mother through a loud speaker in a prisoner's camp. For the NS condition, a fragment from the film "Schindler's List" displaying dead bodies being piled by other prisoners was selected. These films have been previously demonstrated to elicit opposing self-reported ratings of hedonic valence and similarly high levels of emotional arousal (Schaefer et al., 2010). For the CS condition, a video of a woman going up on an escalator and entering a local market was selected. This fragment has been previously used as a neutral stimulus, eliciting low levels of self-reported emotional arousal (Schaefer et al., 2010). With respect to the auditory stimulation, participants listened to "Adagio for Strings" by Samuel Barber and "Divertimento in D Major, K. 136" by Mozart. Both songs have been previously demonstrated to be successful material for the induction of negative (Renner, Schwarz, Peters, & Huibers, 2014); (Werthmann et al., 2014) and positive mood (Eich & Metcalfe, 1989), respectively. Even though some studies have used musical fragments as neutral contents, this strategy is not consensual across the scientific community. It is frequently argued that it is difficult, if not impossible, to use a musical content without an emotional meaning. As such, we decided not to use musical fragment for the CS condition. While one can argue that the sensorial auditory perception *per se* might affect participants' performance during this experiment, we consider this strategy to be the most appropriate, so that we can ensure that there are no consistent effects of an emotional meaning associated with the fragment.

Figure 1. Experimental apparatus. The experience started with a baseline period (60 s), followed by the visualization of an emotional video. Afterwards, participants were presented with the risky decision-making task (the Balloon Analogue Risk Task).

Experimental apparatus

The Balloon Analogue Risk Task (BART) was used for the assessment of risky decision-making. In this task, each trial is comprised of a balloon that can be inflated up to a pseudo-randomly and unpredictably defined threshold. Each inflation is rewarded with points (0.05€)-however, if the balloon explodes, all the points collected during the trial will be lost; on the other hand, if the participant decides to stop inflating the balloon, the accumulated points during the trial will be added to the participants' account. A total of 10 balloons were presented. Each balloon has a randomly varying contingencies, which determined the probability of explosion. A large body of evidence has established reliability of this paradigm across samples and testing conditions (White, Lejuez, & de Wit, 2008).

Following previous recommendations, risk was assessed by examining the adjusted number of pumps (Adj Pumps), *i.e.,* the average number of pumps of the balloons that did not explode. This strategy has been implemented to limit between-subjects' variability in the absolute averages (Lejuez et al., 2002).

Considering the previously reported relationship between risk-taking within the context of the BART paradigm of impulsivity components, namely sensation seeking.(Lauriola, Panno, Levin, & Lejuez, 2014), the Portuguese versions of the UPPS-P was administered to our sample. The UPPS-P (Whiteside & Lynam, 2001) is a 59-item scale, which assesses five dimensions of impulsivity: negative urgency, positive urgency, sensation seeking, lack of premeditation and lack of perseverance. Each item is scored on a Likert scale, ranging from 1 (strongly agree) to 4 (strongly disagree).

A multiple linear regression analysis was implemented to assess the impact of emotional induction on risk-taking behavior (Adj Pumps), while accounting for confounding variables, namely sex and age. Statistical analysis was implemented with both frequentist and Bayesian modelling. Statistical analysis was implemented with R Studio (R Core Team, 2013) and JASP. The dataset and code for analysis is available at the OSF (https://osf.io/4cjmy/).

Results

The descriptive statistics for the BART paradigm are summarized on Table 1. Independently of the experimental condition, there was an average of 6.77 adjusted pumps per balloon (SD=2.24, range: 2.9-13.4) and an average of 4.01 explosions per subject (SD=1.30, range: 2-8).

Table 1. Descriptive statistics for the BART paradigm across experimental conditions

		Mean	Std Deviation	Std Error	Minimum	Maximum	Skewness	Kurtosis
Adjusted Pumps								
	Neutral	7.14	2.51	0.44	3.5	13.4	0.32	-0.69
	Negative	7.23	1.82	0.41	3.86	10.4	-0.29	-1.07
	Positive	6.22	2.17	0.34	2.89	12.5	0.57	-0.22
	All	6.75	2.25	0.23	2.89	13.4	0.35	-0.45
Explosions								
	Neutral	3.94	1.24	0.22	2	6	0.02	-0.97
	Negative	4.05	0.94	0.21	2	6	0.26	0.26
	Positive	4	1.5	0.23	2	8	1.17	0.73
	All	3.99	1.3	0.13	2	8	0.82	0.75

Among the dimensions of the UPPS-P, sensation seeking was the only variable significantly associated with risk-taking, even though the correlation coefficient had a small magnitude (r=.249). Given the prior knowledge of a positive association between impulsivity (particularly sensation seeking) with risk-taking in the BART paradigm, a one-sided hypothesis (*i.e.,* positive correlation) was tested (Table 2, Figure 2). The Bayesian analysis (with a stretched prior width of 1) indicated that H1 is 3.31 times more likely than H0, which according to Jeffreys' classification scheme, represents a moderate evidence for H1 (Jeffreys, 1998).

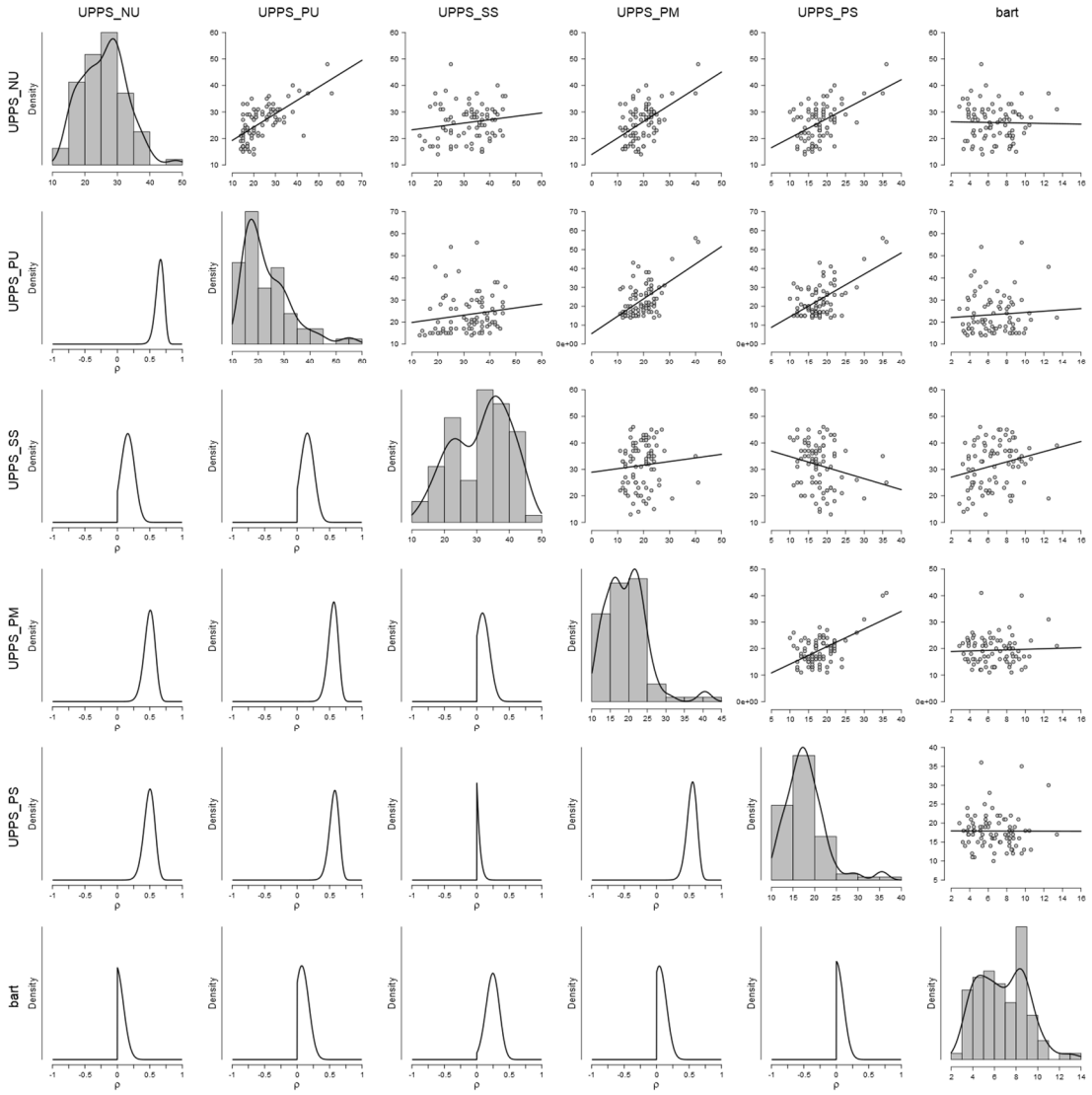

Figure 2. Plots for the correlation matrix reflecting the association between UPPS-P dimensions and the adjusted number of pumps, irrespectively of the experimental condition (upper triangle). The histograms for each individual variable are represented on the diagonal. Posterior distributions under the alternative hypothesis (H1) are displayed on the lower triangle.

Table 2. Correlation between UPPS-P dimensions and the adjusted number of pumps

		UPPS_NU	UPPS_PU	UPPS_SS	UPPS_PM	UPPS_PS
BART	Pearson's r	-0.02	0.072	0.249*	0.042	-0.003
	p-value	0.855	0.523	0.024	0.709	0.98
	UCI 95% CI	0.197	0.284	0.442	0.256	0.214
	LCI 95% CI	-0.236	-0.148	0.034	-0.177	-0.22
	BF_{10}	0.120	0.248	3.306	0.190	0.135

*p<.05; UCI – upper bound for the confidence interval for the correlation coefficient; LCI – lower bound for the confidence interval for the correlation coefficient; BF_{10} – Bayes factor with support for the alternative hypothesis (H1) against the null (H0); a BF_{10} indicates that there is an equal support for H1 as H0. Bayesian analysis was conducted considering a stretched beta prior width of 1.

The results from the multiple linear regression model indicated a statistically significant effect ($F_{(4,76)}$=2.87, p=.029, R^2=.13, R^2_{adj}=.09) for effect of condition, adjusted for sex and age, on risk-taking, *i.e.*, the adjusted number of pumps during the BART paradigm. According to this model, the dummy variable corresponding to the positive emotional induction had a significant negative impact on risk-taking profile (B=-1.58, SE=.60, p=.01). On the other hand, negative induction did not significantly predict risk-taking (B=-.50, SE=.69, p=.47). The regression model is graphically represented on Figure 3. In contrast, no statistically significant effects were obtained for the model predicting the total number of explosions ($F_{(4,76)}$=1.31, p=.275, R^2=.06, R^2_{adj}=.02).

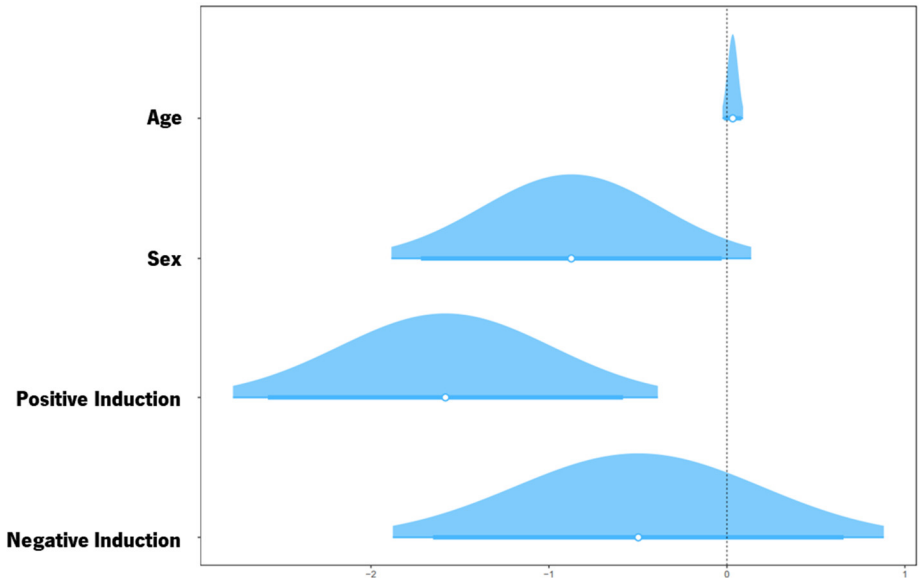

Figure 3. Individual coefficients for the multiple linear regression model. Sex (1 – Female), Positive Induction (1 – Positive) and Negative Induction (1 – Negative) were defined as dichotomic variables. The dashed line represents the threshold for null-effect. Curves represent the rescaled normal distributions for each predictor.

To assess whether this finding would remain in the presence of variables related with impulsive behavior, sensation seeking (the only dimension of the UPPS-P with a significant association with risk-taking) was added to the model. It was observed that this re-specified model was statistically significant ($F_{(5,71)}$=2.74, p=.026, R^2=.17, R^2_{adj}=.11). In this model, we observed that positive induction was the only significant predictor (B=-1.42, SE=.62, p=.026) (Table 3).

Table 3. Linear regression model: Prediction of risk-taking behavior by sociodemographic characteristics, experimental condition and sensation seeking

	B	SE	β	t	p	2.50%	97.50%
(Intercept)	5.907	1.947		3.034	0.003	2.02	9.795
Sex	-0.782	0.538	-0.169	-1.454	0.151	-1.855	0.292
Age	0.036	0.032	0.135	1.136	0.26	-0.027	0.1
Negative Induction	-0.405	0.743	-0.075	-0.544	0.588	-1.889	1.079
Positive Induction	-1.417	0.622	-0.314	-2.279	0.026	-2.658	-0.176
Sensation Seeking	0.057	0.031	0.22	1.857	0.068	-0.004	0.119

B – unstandardized estimate, SE – standard error, β – standardized estimate

As a complementary evidence, the Bayesian linear regression analysis demonstrated that the model comprised by sex, sensation seeking and the dummy variable corresponding to the positive induction yielded the best model (BF_{10}=3.47). Of note, the dummy variable corresponding to the positive induction was among nine out of the ten best models (Table 4). In fact, when considering all the other covariates in the model, the model containing this variable is preferred to the model not including it by a factor 2.88 (Figure 4).

Table 4. Model comparison between the best 10 models.

Models	P(M)	P(M|data)	BF_M	BF_{10}	R^2
Sex + UPPS_SS + dummy_pos	0.031	0.101	3.465	1	0.153
Sex + dummy_pos	0.031	0.099	3.404	0.984	0.121
UPPS_SS + dummy_pos	0.031	0.08	2.702	0.797	0.115
Sex + Age + UPPS_SS + dummy_pos	0.031	0.063	2.088	0.628	0.168
Age + UPPS_SS + dummy_pos	0.031	0.062	2.039	0.614	0.139
dummy_pos	0.031	0.055	1.811	0.549	0.068
Sex + UPPS_SS + dummy_neg + dummy_pos	0.031	0.042	1.35	0.415	0.155
Sex + Age + dummy_pos	0.031	0.041	1.333	0.41	0.126
Sex + dummy_neg + dummy_pos	0.031	0.036	1.172	0.362	0.123
Sex + UPPS_SS	0.031	0.033	1.071	0.332	0.089

P(M) – Probability of predictor; P(M|data) – Probability of the predictor, given the data; BF – Bayes Factor

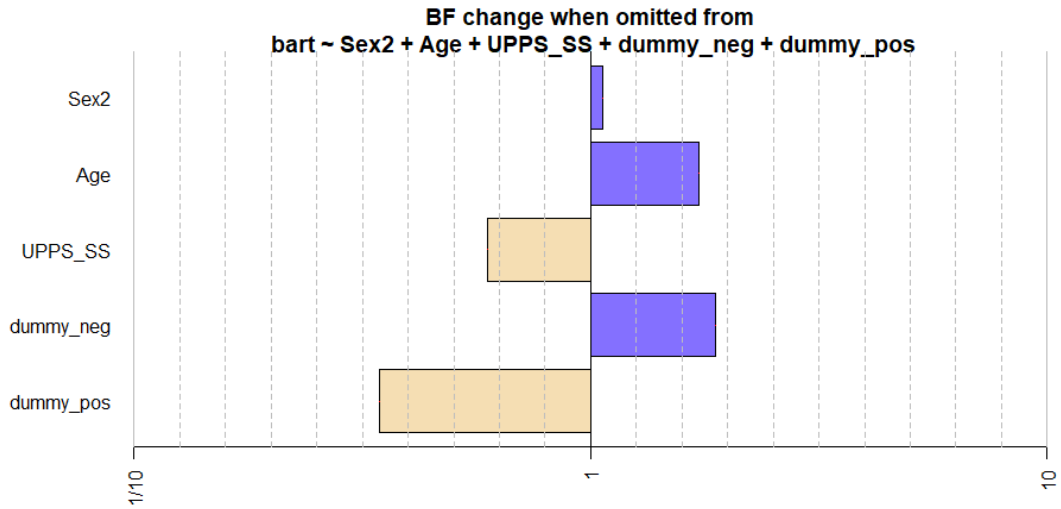

Figure 4. Impact of the deletion of individual predictors on the model.

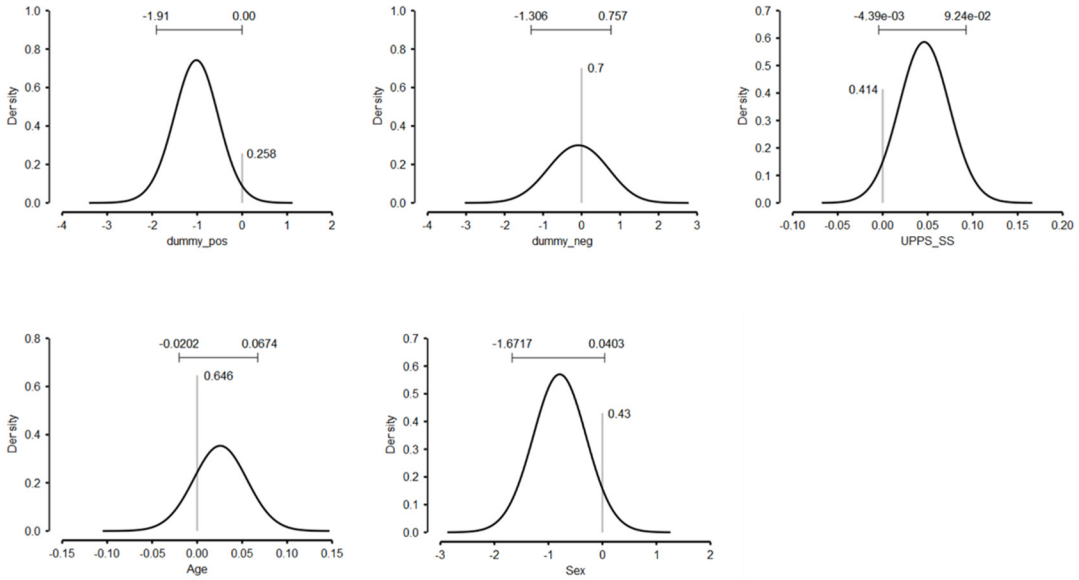

Figure 5. Posterior distribution for each predictor included in the linear regression model, *i.e.,* the knowledge about the effect size obtained after updating the prior distribution using the observed data, assuming that H1 holds. The posterior distribution for the dummy variable corresponding to the positive induction has a median of .258 with a 95% credible interval ranging from -1.91 to 0.00.

The comparison of the risk-taking (i.e., the adjusted number of pumps) is graphically represented on Figure 6.

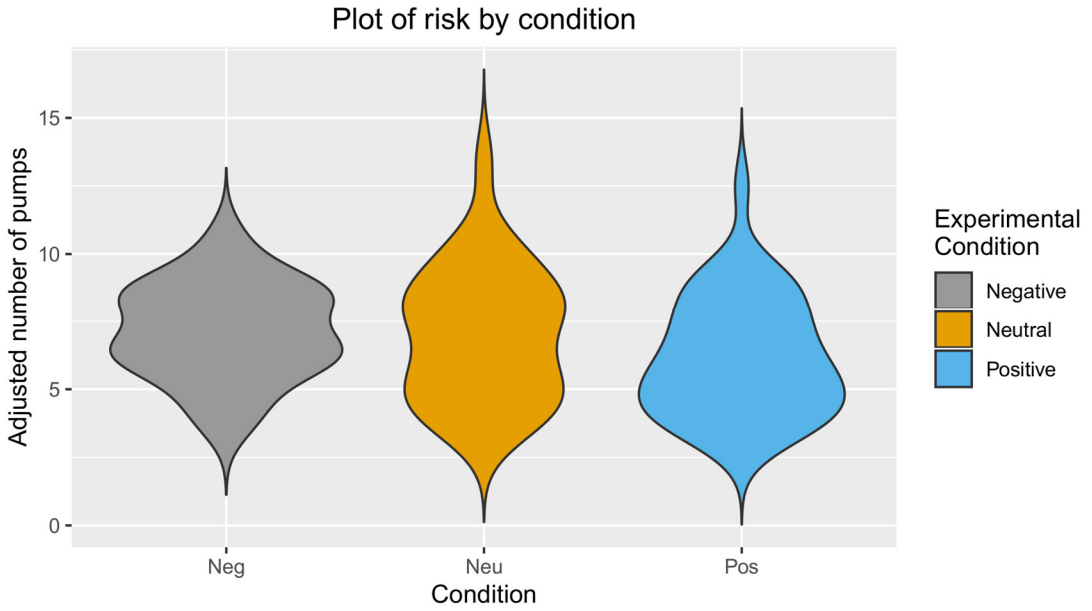

Figure 6. Violin plots representing risk-taking (adjusted number of pumps) by experimental condition.

Discussion

In this work, we assessed the impact of emotional induction on behavioral patterns of risky decision-making. Using previously validated audiovisual stimuli (video and music), we assessed whether positive or negative emotion induction (against neutral stimulation) contributes to altered patterns of decision-making under risk. We observed that emotional condition is associated with risky decision-making profile, even though with a small explained variance. Post-hoc analysis revealed that positive stimuli are characterized by a statistically significant reduced risk-taking during the Balloon Analogue Risk Task (BART) paradigm.

Previous studies have demonstrated that the emotional experience has a relevant role on risky decision-making processing. In fact, humans are able to anticipate the emotional impact of potential future decisions (Bechara et al., 1999). Nevertheless, whereas this relationship has been described, the clear role of emotion on decision-making does not seem to be straightforward. Previous research has demonstrated that the presentation of pleasant arousing cues is associated with an increased preference toward risky economic options in detriment of safer choices (Galentino, Bonini, & Savadori, 2017). In addition, anticipatory positive arousal has been associated with increased risk-taking in a monetary task; on the other hand, when gambling

trails are framed as potential losses, risk-taking appears to be reduced in an experimental condition with positive hedonic valence (Cassotti et al., 2012). Mechanistically, it has been proposed that the activity of the nucleus accumbens (NAcc) responds separately both to anticipatory salience and valence in the context of risky-decision making (Cooper & Knutson, 2008). At the peripheral level, indices of arousal, namely skin conductance have been demonstrated to increase with anticipated gains and losses (Knutson & Greer, 2008).

One aspect that deserves to be noted pertains to the fact that the selection of emotional stimuli was performed based on existent databases of emotionally-loaded stimuli. Whereas we selected these contents, based on matching levels of emotional arousal, with opposing levels of hedonic valence, the self-reported valence and arousal was not obtained in our sample. While our strategy values large-scale validation of these stimuli as adequate tools for emotional induction, which maximizes the comparability between studies in different contexts, it may be also be susceptible to sample-to-sample variation. As such, one stimulus being selected for eliciting high levels of arousal may (due to sociocultural characteristics, for instance) may elicit only moderate levels of arousal on the target sample – which may modulate the impact of these stimuli on behavioral patterns of risk-taking behavior. Another issue pertains to the fact that we favored a control for the contextual characteristics of the video stimuli, so that the main differences between the stimuli were mainly driven by the emotional experience and not by other systematic effects. In addition, the selection of these contents was also motivated by the fact that both represent cinematographic productions with approximate notoriety (La vitta et bella and Schindler's List). This also reduces the likelihood of systematic effects of familiarity on the provocation of the target emotional experience.

Whereas this study provides relevant insight regarding the impact of emotional induction on behavioral patterns of risky decision-making, we consider that it is worthwhile to assess these aspects at a more mechanistic level. More specifically, future studies may address how the induction of negative or positive emotional states impacts on neurobiological responses during decision-making performance. For this purpose, studies using modalities such as functional magnetic resonance imaging (fMRI) may provide additional value for a better understanding of how the induction of emotional states affect risky decisions.

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Chapter 5. General Discussion

In this work, we developed a comprehensive assessment of the dynamics of decision-making, by characterizing their neurobiological mechanisms, their pathological manifestations and how the induction of an emotional state interferes with such processes. This investigation was conducted throughout the use of primary, empiric research, as well as by focusing on secondary research, in which we relied on the use of meta-analytic approaches for making the bridge between emotion and decision-making behavioral profiles.

On Chapter 1, we summarized the neuroimaging literature focusing on distinct modulators of goal-directed decision-making, namely risk and uncertainty, delay discounting and social modulators. In this aggregation, we highlighted that individuals do not typically rely on economic or rational approaches when making decisions. Based on empirical contributions from decades of scientific research, we reported that individuals present consistent deviations from rational models of choice. Nevertheless, the same individual is likely to engage in inconsistent patterns of choice when assessed in separate moments with similar choice scenarios. These frequent deviations from purely maximization expected utility perspectives are present across different types of decisions. At the neurobiological level, even though disparate modulators of goal-directed decision-making are characterized by unique patterns of consistent brain activation, there are common neurobiological substrates underlying different modulators of the valuation systems of decision-making processing. These findings seem to suggest that humans are characterized by partially overlapping neurobiological responses when having to decide, independently of the decision-making scenario. Relevant nodes for these processing include, among others, different divisions of the insula, striatal regions and prefrontal cortex.

On Chapter 2, we focused on the characterization of OCD, a psychiatric disorder characterized by chronic levels of stress (Appendix D), which has been described as a disorder of decision-making (Cavedini, Gorini, & Bellodi, 2006; Sachdev & Malhi, 2005). The findings obtained throughout the chapter indicate that OCD is characterized by a set of brain alterations, both with respect to intrinsic features (*i.e.,* brain structure and rs-FC) and to functional patterns of brain activation during the anticipation and feedback phases of risky decision-making. On Chapter 2.1, we observed that OCD patients are characterized by a set of structural and functional brain alterations. Using a voxel-based morphometry approach, we reported that these patients are characterized by significantly reduced volumes of the middle temporal gyrus. With regards to rs-FC, in comparison with healthy individuals, patients displayed statistically significant

reduced FC in two sub-networks: the first involving bilateral nodes from the orbitofrontal cortex (OFC) and the temporal poles; the second comprised of edges connecting sensorial and occipital nodes. On the other hand, OCD was characterized by significant increases of rs-FC in a network comprised of edges connecting thalamic nodes to parietal and occipital brain regions. A complementary approach based on independent-component analysis revealed that patients are characterized by altered FC within and between distinct resting-state networks: patients had significantly reduced FC within visual (primary and secondary) networks and within a sensorimotor network; furthermore, patients displayed reduced connectivity between primary and sensorimotor networks and increased connectivity between a component of the default-mode network and the cerebellar network (Chapter 2.2). A further consideration pertains to a novel characterization of the FC dynamics within these patients. To the best of our knowledge, our preliminary findings (Appendix C) provide unique evidence for the study of spontaneous occurrence of states of dFC. Using a leading-eigenvector analysis (Cabral et al., 2017), we observed that OCD patients are characterized by a significantly decreased probability of occurrence of an FC state, representing a Limbic-Striatal-Cerebellar network and a Fronto-Parietal-Cerebellar network. On the other hand, a baseline state of global FC coherence was found to have an increased probability in the group of OCD patients.

On Chapters 2.3 and 2.4, we noted that even though OCD patients display a risky decision-making profile comparable with healthy controls, their behaviors seem to be governed by distinct neurobiological mechanisms. This notion is supported by the fact that the structure of key regions for the processing of reward – namely striatal regions – are associated with the risk profile of healthy individuals, but not for OCD patients (Chapter 2.3). In addition, when anticipating risky decisions, OCD patients display significantly reduced activation of anterior and posterior cingulate regions, as well as an altered modulation of the amygdala in response to high-risk choices (Chapter 2.4). Together, these results seem to suggest that there is an altered processing of expected and obtained reward – which may be affected by a disturbed sensory-limbic integration. An impaired emotional processing has been widely described as one of the core features of OCD (Thorsen et al., 2018), being these individuals characterized by attentional biases to threat stimuli (Thomas, Gonsalvez, & Johnstone, 2013). Departing from the results of a recent meta-analysis, we demonstrated that the consistent patterns of increased brain activation in OCD patients are functionally connected with key regions that are of upmost relevance for decision-making processing, such as the insular cortex, striatum and prefrontal

brain regions (Chapter 2.5). If we adopt an integrative perspective on the findings reported in Chapter 2, we can observe a considerable overlap between the altered brain patterns in OCD and the "pleasure systems in the brain" (Berridge & Kringelbach, 2015).

On the other hand, the involvement of occipital regions on the pathophysiology of the disorder is considerably underexplored on the scientific literature. Recent publications have emphasized the role of visual systems for the pathophysiology of different psychiatric conditions, such as neurodevelopmental conditions (Laycock, Crewther, & Crewther, 2007), schizophrenia (Butler & Javitt, 2005), bipolar disorder (Shaffer et al., 2018). Even though there has been previously hypothesized that abnormal functioning of occipital areas may contribute for some features of the disorder (Gonçalves, Marques, Lori, Sampaio, & Branco, 2010), future research is needed to further elucidate on the complex interaction between the visual system and limbic areas during task performance.

It is well established that OCD is not a homogeneous psychiatric disorder – rather, it is characterized by a complex variation of the clinical profile, co-morbidity, and therapeutic responses (Leckman, Rauch, & Mataix-Cols, 2007), with dissociable neurobiological characteristics (Robbins, Gillan, Smith, de Wit, & Ersche, 2012). As an example, we demonstrated that obsession and compulsions have distinct correlates at the brain network level (Appendix B). Therefore, a further clarification of distinct manifestations of the disorder, by contrasting different subtypes of the disorder (*e.g.,* patients characterized by contamination obsessions versus patients with checking obsessions) is still needed to better understand the neurobiological idiosyncrasies of distinct clinical profiles. This examination may have a direct impact on a better delineation of treatment interventions for each individual patient. Other issue that deserves further exploration pertains to the influence of medication on decision-making in these individuals. Most patients included in our analyses were receiving pharmacological treatment, namely selective serotonin reuptake inhibitor (SSRI) interventions. It remains an open question whether the inclusion of drug-naïve patients would lead to more pronounced differences in decision-making processing in comparison to healthy individuals. Previous studies have highlighted the SSRI treatment contributes to significant structural and functional brain alterations, such as reductions of the thalamic volume (Gilbert et al., 2000), reductions of the functional activity in fronto-subcortical regions (Nakao et al., 2005) and restorations of whole-

brain functional connectivity, as demonstrated by elevations of small-word efficiency, modular organization and degree (Shin et al., 2014).

The emotional experience is characterized by a set of central and peripheral responses. The state-of-the-art has repeatedly demonstrated that there is a great dependency between the emotional experience and decision-making processing. Specifically, it has been demonstrated that brain regions that are recruited for emotional experience, are also involved in decision-making processing, such as the vmPFC (Hiser & Koenigs, 2018). This has been also supported by the fact that the neurobiological mechanisms underlying the emotional processing in OCD are part of a network of functionally connected nodes involved in decision-making processing (as we report on Chapter 2.5). A popular theoretical model - the somatic marker hypothesis – posits that the process of decision-making frequently involves some degree of uncertainty and that the decisions under these scenarios are supported by emotions in the form of bodily states (Naqvi, Shiv, & Bechara, 2006) – even though this view was previously criticized (Dunn, Dalgleish, & Lawrence, 2006; Maia & McClelland, 2004).

Whereas we did not find evidence for emotional specificity on peripheral responses, we did find that the perceived intensity (*i.e.,* self-reported arousal) of the emotional induction is associated with the magnitude of peripheral responses, namely from the electrodermal and cardiovascular systems (Chapter 3.1). The lack of emotional specificity was also previously demonstrated in a recent meta-analytic aggregation of neuroimaging studies (Lindquist, Wager, Kober, Bliss-Moreau, & Barrett, 2012). However, using a connectomics approach, we observed that the experience of contrasting affective states with similar levels of perceived arousal is associated with static and dynamic FC alterations (Chapter 3.2).

Emotion is proposed to be a critical component of individual traits, such as impulsivity (Whiteside & Lynam, 2001), which directly impacts on our decision-making behavior (Chapter 4.1). This conceptualization favors a multidimensional (orthogonal) perspective of impulsivity, which besides emotion-based rash action, also includes the characterization of sensation seeking and deficits in conscientiousness in the assessment of impulsivity (Whiteside & Lynam, 2001). These different components have been described to have dissociable associations with external constructs, such as risk-taking (Canale, Rubaltelli, Vieno, Pittarello, & Billieux, 2017) or reward sensitivity (Kale, Stautz, & Cooper, 2018). In our work, we observed that two of these dimensions,

lack of perseveration and negative urgency, are significantly associated with resting-state whole-brain FC (Chapter 4.1).

A relevant aspect concerns the role of impulsivity in OCD patients. Although impulsivity and compulsivity are traditionally considered opposite poles of a continuous spectrum (Hollander, 2007), the association between these constructs does not appear to be straightforward (Grant & Kim, 2014). These two dimensions frequently originate similar behavioral deficits associated with failures of "top-down" cognitive control (Dalley, Everitt, & Robbins, 2011). However, the mechanism of action of these two dimensions is thought to be influenced by different mediators: whereas impulsivity is related with the tendency to act by impulse, compulsivity is related with the problem of terminating actions (Dalley et al., 2011) (Grant & Kim, 2014). In the case of OCD, the relationship between these constructs is characterized by a complex framing. It was recently demonstrated that OCD patients can be grouped into different clusters on measures of impulsivity and compulsivity: patients with low levels of impulsivity and compulsivity; two clusters of patients with similar clinical severity, but with opposing drivers (*i.e.,* high compulsivity and low impulsivity, and vice versa); the last cluster was characterized by high levels on both constructs – which was also the group with highest clinical severity (Prochazkova et al., 2018). This supports the view that the relationship between these may be somehow overlapping constructs under specific conditions (Robbins et al., 2012). Future studies may yield further clarifications regarding the association between impulsivity and OCD.

Even though the emotional experience does not seem to be specific for individual emotional categories – *i.e.,* there is little evidence for a neurobiological signature for each category – the induction of an affective state does seem to be associated with individuals' preparation for action. We observed that contrasting hedonic valences seem to differentially impact decision-making behaviors across different behavioral modalities, such as a diminished risk-taking behavior following the induction of positive arousal (Chapter 4.2). However, it is worth mentioning that these results should be interpreted with caution, given the variation of the level of evidence of the estimated in robustness analyses.

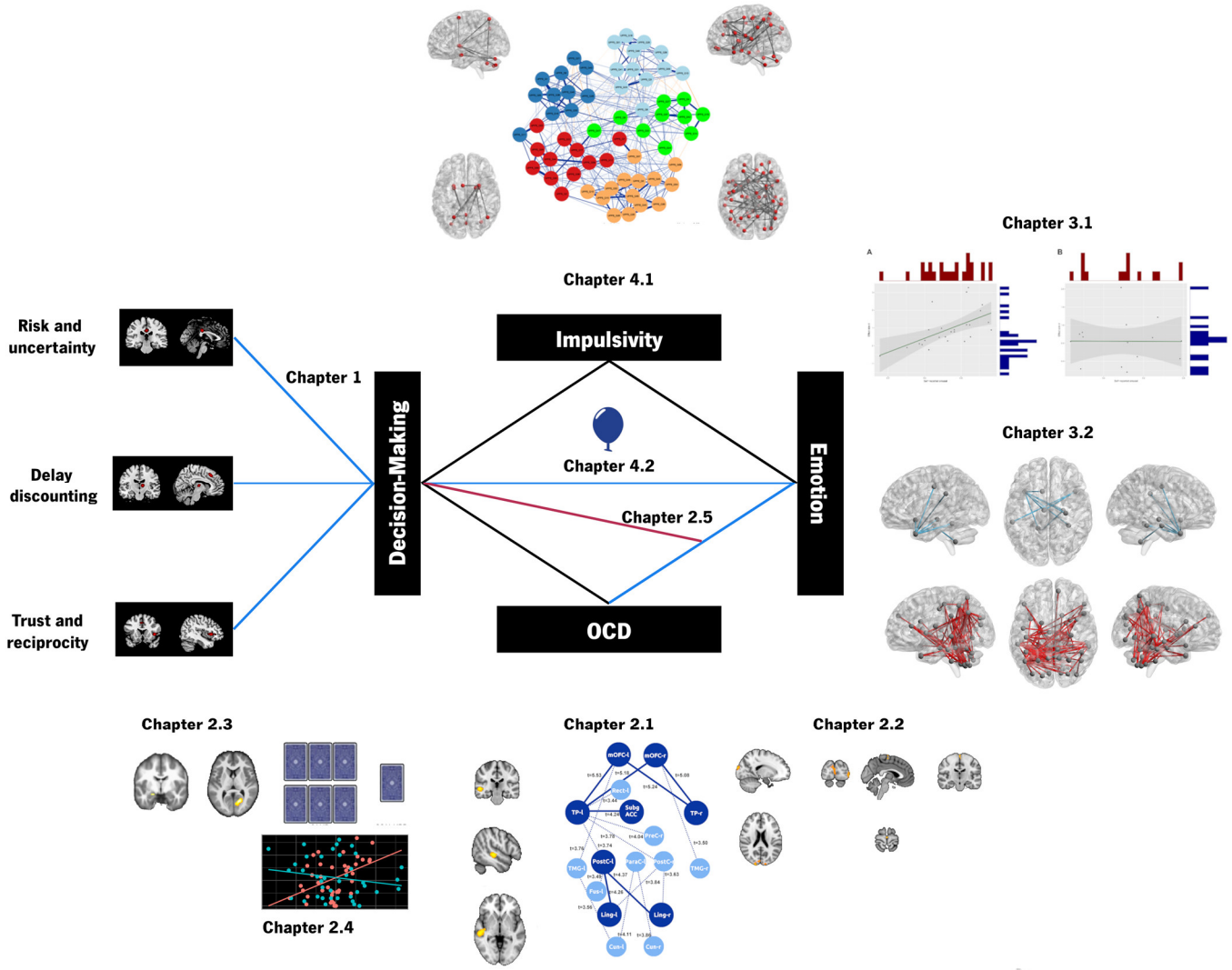

Figure 1. Summary of the topics approached in this thesis. This work focused on four main topics. Our main goal was to characterize the neurobiological mechanisms underlying decision-making. For this purpose, we provided a comprehensive characterization of the neurobiology of obsessive-compulsive disorder (OCD) – which has been repeatedly advocated to represent a disorder of decision-making processing – with respect to the intrinsic patterns of brain structure and function and with regards to the neurobiological responses associated with risky decision-making. Given the relevance of emotional processing for decision-making capacity and given the fact that these patients are characterized by impaired emotional responses, we approached the overlap between the meta-analytic maps of emotional processing in OCD and how they are linked to the neurobiological mechanisms involved in decision-making processing. We next explored how the emotional processing impacts central and peripheral nervous systems' correlates and characterized the role of emotional dimensions on impulsive behavior and, namely how it affects decision-making under risk.

Future perspectives

There are several relevant questions that were not tackled in the context of this work and that provide opportunities for further investigation on this topic. One first aspect is related with the use of the multimodal data to better understand the complex interaction between structure, intrinsic function and task-related patterns associated with decision-making processing. As we previously highlighted, the risky profile of OCD patients seems to be independent of the structure of brain regions of the valuation system. Nevertheless, it is also important to identify whether there are some complex association between brain structure and function that compensates this abolished association.

A more domain-related issue is associated the narrow approach of decision-making that was tackled in this investigation. Even though we started by characterizing different domains of decision-making, involving different value modulators (delay discounting, risk and social modulators), our empirical neuroimaging investigation was mainly focused on the study of risk processing. In the future, we intend to extend our line of research to capture other domains of decision-making, particularly social decision-making.

Another issue pertains to a more fine-grained characterization of how the affective experience affects the neurobiological processing underlying decision-making processing. It is not a new idea that emotions play an important role in how we make decisions. As such, even though we could observe that the induction of affective states is associated with a set of central and peripheral biological alterations and that affective dimensions of impulsive behavior are associated with the brain connectome, we consider that the characterization of this interference during task performance remains an important open issue.

For that purpose, future investigations may tackle how the induction of dissociable affective states with varying intensity impacts not only the behavioral patterns of decision-making, but also how it affects the neurobiological responses leading to these decisions. It is of upmost relevance to characterize not only how individual brain regions are differentially recruited under emotional states, but also to account for the patterns of synchronization between different brain areas while individuals decide. For that purpose, the use of analytic approaches such as

psychophysiological interactions or dynamic causal modelling may provide us with a better understanding of functional and effective connectivity correlates of decision-making in healthy and in pathological conditions.

Furthermore, the recent emergence of dynamic approaches to characterize how the brain shifts from distinct connectivity states also raises promising new perspectives. While this recent trend has been mainly tackling the FC dynamics during resting-state, understanding how task-related demands contribute to the occurrence and shifting between spontaneous FC states constitutes an exciting avenue for future research. In the context of our work, such approach may help to better characterize how these dFC fluctuations contribute to more or less optimal decisions both in healthy and in OCD patients. By better understanding what leads to these dynamics fluctuations and by being able to model the brain as a system – so that it can be characterized by "more optimal" dFC patterns – the neuroscience field can have a special role on the development of interventions that may provide more effective interventions in the neuropsychiatric context. This optimistic view is supported by recent advances in the field of computational connectomics, which is aimed to model resting-state and task-related brain dynamics in health and disease (Deco & Kringelbach, 2014). Such approach is expected to be a key player on the development of drugs with more focused targets, the identification of mechanisms for brain stimulation or for neurofeedback may lead to a change in the paradigm in the treatment of psychiatric disorders.

In sum, although this work has contributed to an extension of the knowledge of the neurobiology of decision-making in healthy and pathological conditions, there is a long journey to follow.

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APPENDICES

APPENDIX A

Identifying Functional Subdivisions in the Medial Frontal Cortex

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Identifying Functional Subdivisions in the Medial Frontal Cortex

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Review of de la Vega et al.

The medial frontal cortex (MFC) is thought to be involved in numerous sensorimotor, cognitive, and affective processes. This region is commonly divided into separate subregions, including the anterior cingulate cortex, supplementary motor area (SMA), and the pre-SMA, orbitofrontal cortex, and anterior frontal poles (Amodio and Frith, 2006). The activity of the MFC is highly heterogeneous. Activation of the MFC is reported in many fMRI studies, and it is associated with a variety of processes, including action monitoring (Bonini et al., 2014), response conflict (Gehring and Fencsik, 2001), reward (Taylor et al., 2006), and decision-making (Kahnt et al., 2011). This creates uncertainty in the identification of specific psychological states associated with patterns of activity in the MFC, referred as the reverse inference problem. This long-standing inferential problem arises because most neuroimaging studies aim to identify neural characteristics of specific manipulations, rather than determining which psychological states a given pattern of activity implies (Poldrack, 2006). The ability to perform reverse inferences is of upmost relevance for the fMRI research to establish a diagnostic of a particular state (i.e., to provide significantly greater specificity to neuroimaging findings), which is crucial for advancing our understanding of the mind and brain (Poldrack, 2006).

In a recent publication in *The Journal of Neuroscience*, de la Vega et al. (2016) sought to extend knowledge of the functional architecture of the MFC by performing a meta-analysis of ~10,000 studies from the Neurosynth platform, a large-scale database with automated synthesis of neuroimaging data (Yarkoni et al., 2011). Based on patterns of coactivation, the authors found that aggregating MFC voxels into three or nine divisions yielded the best clustering solutions. The tripartite organization divided the MFC in posterior, middle, and anterior zones. The 9-cluster solution further divided these zones into dissociable subregions: the posterior zone was divided into the supplemental motor area (SMA) and the pre-SMA; the middle zone, or midcingulate cortex, was divided into dorsal/ventral and anterior/posterior subregions; and the anterior zone was separated into dorsomedial prefrontal cortex, ventromedial prefrontal cortex (vmPFC), and pregenual anterior cingulate cortex. These zones presented distinct coactivation patterns with the remaining brain structures: the posterior zone was mainly associated with motor-related regions; the middle zone with the anterior thalamus and clusters from the frontoparietal control network; and the anterior zone with clusters from the Default-Mode Network. Finally, the authors modeled the topics of each study in the Neurosynth database and generated functional preference profiles by testing which topics from the semantic context of each study best predicted the activation of a given region, using a Bayesian classification approach. The activation of the posterior zone was associated with motor functioning; the middle zone with cognitive control, pain, and affect; and the anterior zone with reward, social processing, and episodic memory.

These results are complemented by the parcellation of the human cerebral cortex recently proposed by Glasser et al. (2016). One of the most prominent differences concerns the anterior part of the MFC, particularly the vmPFC, which was divided into more subregions in the Glasser et al. (2016) study (mainly associated with Default-Mode Network clusters). These differences might arise from methodological considerations pertaining to the strategy of parcellating the MFC. In the study from de la Vega et al. (2016), the 9-cluster

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solution was selected due to the stabilization of the silhouette coefficient (the minimum average distance between cluster members). However, no point of inflection was observed, opening the possibility that the maximum number of clusters considered (15) might not be enough to reveal more refined subdivisions of the MFC. It can be hypothesized that the vmPFC is composed of subregions that have distinct roles at rest, but function in coordination during affective processes, such as reward or fear. Indeed, when analyzing the results from de la Vega et al. (2016, their Fig. 4), it is evident that, although distinct subdivisions of the anterior MFC are indissociably linked to episodic memory, they are differently associated with reward. Therefore, it is reasonable to assume that these subdivisions may work either together or separately, depending on the functional context. Furthermore, it is also likely that regions with different properties, such as the ones explored by Glasser et al. (2016), coexist across psychological states by making part of the same circuit. Of note, none of the studies integrated structural connectivity for the parcellation of the MFC, which is thought to influence brain functional patterns (Park and Friston, 2013). Together, this suggests that the cortical organization of the MFC is still an open question and further developments can be expected in the near future.

de la Vega et al. (2016) suggest that the association of SMA with pain processing and motor function could reflect the importance of this region for initiating movement in response to pain. This is in accordance with previous reports of associations between activation in the SMA, motor control, and painful stimuli (Misra and Coombes, 2015). Despite falling within the same cluster for the tripartite solution, posterior subdivisions have dissociable structural links: whereas the SMA projects directly to motor areas, the pre-SMA projects to the dorsolateral prefrontal cortex (Wang et al., 2005). However, there seems to be no clear functional dichotomy or clear structural boundary between the SMA and pre-SMA subdivisions, but rather a continuum that does not favor a modular organization (Nachev et al., 2008).

de la Vega et al. (2016) also suggested that the dorsal clusters from the middle zone were more associated with cognitive motor control that requires working memory, whereas the ventral clusters' function would be to incorporate low-level affective signals into cognitive control. Despite agreeing with previous findings reporting an involvement of the mid-cingulate cortex in pain processing (Vogt, 2016), these results seem to suggest that dorsal clusters share functional commonalities with the posterior MFC, whereas anterior subdivisions are more related with the anterior MFC. Again, this raises the question of the extent to which the MFC should be considered as an agglomerate of functionally distinct subparts and whether the functional division depends on the functional context. Critically, de la Vega et al. (2016) suggest that the anterior zones of the MFC (particularly the pregenual anterior cingulate cortex and the vmPFC), in comparison with other MFC subdivisions, are more associated with affective processes and decision-making. This supports the view of Euston et al. (2012) that the role of the anterior MFC is to produce adaptive emotional responses based on inputs from emotion-related structures and storing the appropriate actions.

Some methodological points should be considered. The authors used generative topic modeling to define a set of topics based on the co-occurrence of key words across the abstracts of fMRI studies. de la Vega et al. (2016, their Table 1) demonstrated some words loaded on multiple topics (e.g., "cognitive" loaded on three topics: conflict, inhibition, and working memory), which may explain why all the subregions of the middle portion of the MFC were similarly predicted by inhibition and response conflict (de la Vega et al., 2016, their Fig. 4). As recognized by the authors, the use of standardized ontologies (e.g., Poldrack et al., 2011) might constitute an improvement on the reliability of psychological concepts. Ultimately, this may help to further clarify the link between individual subregions of the MFC and their functional correlates.

Despite the valuable efforts of the study by de la Vega et al. (2016) to address the reverse inference problem associated with the MFC, it is important to be aware that their conclusions were based on forward inferences. Thus, future studies should focus on predictive models in which psychological states are classified based on the pattern of activation of individual MFC subdivisions, rather than using the psychological states to predict patterns of MFC activity. This would allow researchers to properly tackle reverse inferences (i.e., to infer that the pattern of MFC activation affects a specific function).

Recent debates in fMRI research have focused on the huge rate of false positive findings (Eklund et al., 2016) and the reduced chance of results' reproducibility (i.e., statistical power) (Button et al., 2013). Although scarcely used in fMRI research, the use of planned power analysis may improve the level of evidence in this type of study (Mumford, 2012). Notwithstanding, as de la Vega et al. (2016) highlight, the meta-analytic approach implemented in their study was exclusively based on the aggregation of results reported as significant across studies. This is because the results of most neuroimaging publications are presented as tables with the coordinates of significant findings, which can be particularly problematic because it is likely that subthreshold, but consistent, effects across studies will not be captured when aggregating results (Gorgolewski et al., 2015). Thus, this work highlights the importance of sharing full statistical maps in individual neuroimaging studies to allow more refined estimation, through the use of image-based meta-analysis.

In conclusion, the study by de la Vega et al. (2016) is an important advancement in our understanding of the functional architecture of the MFC. Furthermore, it provides a great incentive for the development of strategies to solve a common concern in fMRI studies: the reverse inference problem. From a general perspective, the use of similar approaches may promote a more comprehensive understanding of the link between brain structures and their functional role, which is of upmost relevance to illuminate potential therapeutic targets in clinical populations.

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APPENDIX B

Distinct contributions of obsessive and compulsive symptoms for whole-brain functional connectivity in obsessive-compulsive disorder

Moreira PS, Marques P, Magalhães R, Soares JM, Sousa N, Morgado P

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strategy – 50% responders had repressive coping style, 36% were high-anxious.

Conclusion: The same intervention toward trauma may cure or harm depending on the time of administration. In Ukraine, there was no evidence based studies proving or disproving harm of early administration of BZD right after exposure to trauma. We anticipate that SSRI can reduce the risk of developing PTSD, or even prevention of administration of BZD will improve whole situation.

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P.4.b.017 The evaluation of motor cortex excitability measures in patients with obsessive–compulsive disorder

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Introduction: Until today, there have been several biological hypotheses concerning the pathophysiology of OCD and many drug, brain imaging and electrophysiological investigations supporting these hypotheses [1–4]. The number of electrophysiological studies in OCD are quite insufficient and the data concerning with the cortical excitability seem considerably controversial [5–8].

Aim: The aim of the present study is to investigate whether there would be differences in the motor thresholds and other excitability measures between OCD patients and healthy controls in a large sample, without excluding comorbidity and medication use.

Method: A total of 32 OCD patients and 21 healthy volunteers were included in the study. The axis I disorders of all subjects were evaluated structured interview with MINI. Any volunteers with axis I disorder and/or alcohol and substance use disorders were excluded from the study. All the subjects were evaluated by Y-BOCS, HAM-D, HAM-A, CGI, BDI and VAS scales simultaneously with the electrophysiological procedures. RMT, SICI, ICF and LICI parameters of cortical excitability were determined by stimulating the left motor cortex.

Findings: The main findings of the present study were that RMT measures were not significantly different between the healthy volunteers and OCD patients, but were significantly increased in the patient subgroups with comorbid major depression and with severe illness.

Conclusion: In our study, no significant difference was detected in cortical excitability measures between the healthy subjects and OCD patients. This finding may either be due to a bias in the selection of the healthy subjects or the potential methodological differences between our study and the previous ones [5–7]. Also, it may result from comorbid disorders or the medications. Therefore, it is important selecting the electrophysiological methodology and considering the comorbidity for the future studies of cortical excitability in OCD.

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P.4.b.018 Distinct contributions of obsessive and compulsive symptoms for whole-brain functional connectivity in obsessive-compulsive disorder

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Background: Obsessive-compulsive disorder (OCD) is one of the most disabling psychiatric conditions, impacting occupational, academic and social functioning [1]. The symptomatology of OCD relies on two major dimensions: obsessions, which consist of the occurrence of persistent and intrusive and, frequently, inappropriate thoughts, causing an extreme anxiety to these patients; and compulsions, which can be described as a set of ritualistic, repetitive, behaviors that are conducted to reduce the anxiety elicited by the obsessive thoughts [2]. Several reports have characterized the patterns of structural and functional connectivity in these patients, mainly focusing the structural and functional integrity of the cortico-striatio-thalamic-cortical (CTSC) brain circuits. It has been described that OCD patients exhibit several paths with significantly decreased functional connectivity, including: connections between the dorsal striatum and the lateral prefrontal cortex, between the ventral striatum and the ventral tegmental area, between dorsal ACC and right anterior operculum FC during rest [3]. Furthermore, FC reductions of specific resting-state networks have been highlighted. Among this, it was reported that the FC between the default-mode network (DMN) and the orbitofrontal cortex, anterior cingulate cortex, middle frontal gyrus and putamen is significantly reduced in OCD patients [4]. Nevertheless, the FC markers of obsessive and compulsive features are still underexplored in the literature. With this purpose, we conducted a neuroimaging investigation to study the functional connectome of these two different dimensions of the disorder.

Methods: The diagnosis of the disorder was performed by experienced psychiatrists, using a semi-structured interview based on Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)-TR in a sample of 40, medicated, OCD patients. This diagnosis was complemented by a clinical assessment of

the severity of obsessive and compulsive symptoms, though the Yale–Brown Obsessive–Compulsive Scale (Y-BOCS [5]). Functional MRI scans using echo-planar imaging (EPI) sequences with blood-oxygen-level-dependent (BOLD) contrast were obtained, while patients were at rest. The whole-brain functional connectome, derived from resting-state functional connectivity (FC), was analyzed with the Network-Based Statistic methodology, considering $\alpha = 0.0005$ as the threshold for statistical significance.

Results: Results from the whole-brain functional connectome analysis revealed dissociable contributions from obsessive and compulsive symptoms to FC patterns. The severity of compulsive symptoms was negatively and significantly associated ($p = 0.047$, non-parametric permutation testing) with a main network comprised of connections, in which the right pallidum was a central node, forming edges with frontal (inferior frontal gyrus), occipital (lingual and calcarine, bilaterally) and cerebellar brain regions. No significant associations were found for the severity of obsessive symptoms.

Conclusions: The results of this study suggest that whereas compulsive thoughts are accompanied by specific patterns of brain functional connectivity, no significant associations for obsessive thoughts were found. These findings provide additional evidence that obsessions and compulsions could be mediated by distinct neuronal networks. Future studies should extend the finding herein obtained, mainly through the integration of structural findings (e.g., volumetric, cortical thickness and diffusion data) as a means to further explore the distinct neural correlates of obsessive and compulsive symptoms.

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P.4.c Anxiety disorders, OCD, stress related disorders and treatment – Treatment (basic)

P.4.c.001 Common neurotransmission recruited in (R,S)-ketamine and (2R,6R)-hydroxynorketamine-induced sustained antidepressant-like effects

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Racemic (R,S)-ketamine, at sub-anesthetic doses, exhibits a rapid and persistent antidepressant activity in treatment-resistant depressed patients and in preclinical studies in rodents [1]. (R,S)-ketamine also induces stress resilience [2]. However, the molecular and cellular mechanisms mediating these activities are unknown. (R,S)-ketamine, a non-competitive antagonist of N-methyl-D-aspartate receptor (NMDA-R), unlikely exerts its antidepressant-like activity solely via a blockade of this ionotropic receptor. We recently reported that (R,S)-ketamine-induced increases in presynaptic serotonin (5-HT) release in the medial prefrontal cortex (mPFC) correlated with its antidepressant-like activity in mice [3]. The control exerted by the mPFC is important in regulating stress processing and antidepressant-like activity. However, little is known about the regulation of synaptic excitatory/inhibitory balance and concomitant changes in glutamate/γ-aminobutyric acid (GABA) neurotransmission induced by (R,S)-ketamine or its metabolites in rodent mPFC.

Recently, it was shown that (R,S)-ketamine metabolism to (2R,6R)-hydroxynorketamine (HNK) is essential for its antidepressant-like activity, and involves early activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA-R) in mice hippocampus and mPFC [4]. However, (R)-ketamine displays greater potency and longer lasting antidepressant effects than (2R,6R)-HNK [5]. Brain tissue concentration of (2R,6R)-HNK is about 25% of that of (R,S)-ketamine [4], but brain regions and neurotransmitter systems supporting (2R,6R)-HNK effects are unknown.

Here, we compared the sustained antidepressant-like activity and neurotransmitters' changes between (R,S)-ketamine and (2R,6R)-HNK in BALB/cJ mice, using the forced swim test (FST), a model to screen antidepressant-like activity of drug, coupled to in vivo microdialysis **in the same mice**. Cortical extracellular levels of 5-HT, GABA, glutamate and glutamine were measured by HPLC coupled to either an electrochemical detector or mass spectrometry. The data were analyzed using one-way ANOVA followed by Fisher's PLSD post hoc test.

A single dose of (R,S)-ketamine and (2R,6R)-HNK (10 mg/kg, intraperitoneal, or 1 nmol/side, perfused locally intra-mPFC) administered 24 hr prior testing showed comparable antidepressant-like activity in the FST and cortical serotonergic effects (i.e., significantly increased three-fold and two-fold, respectively, compared to vehicle, all $p < 0.05$). Interestingly, (2R,6R)-HNK displayed a more glutamatergic potency than (R,S)-ketamine (+150% higher than vehicle, $p < 0.05$, vs + 114%, $p > 0.05$, respectively), while (R,S)-ketamine increased more GABA release than (2R,6R)-HNK (+63% higher than vehicle, $p < 0.05$, vs + 35%, $p > 0.05$, respectively).

In conclusion, we found that: (i) both (R,S)-ketamine and (2R,6R)-HNK administered at equivalent doses displayed a sustained antidepressant-like activity in mice and independently exert this activity via NMDA-R blockade and AMPA-R activation, respectively; (ii) Presynaptic cortical release of various excitatory and inhibitory neurotransmitters is required for this activity, which may have long lasting consequences; (iii) (2R,6R)-HNK increased excitatory synaptic transmission in the mPFC by enhancing presynaptic glutamate release; and (iv) (2R,6R)-HNK complements neurochemical effects of (R,S)-ketamine in the mPFC. We need now to clarify the mechanism of action of (R,S)-, (R)- or (S)-ketamine and (2R,6R)-HNK by studying the cellular and molecular events modulating their activity in the mPFC, and to

APPENDIX C

Disrupted Functional Connectivity Dynamics in Obsessive-Compulsive Disorder

Moreira PS, Costa PC, Sousa N, Soriano-Mas C, Morgado P, Cabral J

Abstract Submitted to the Annual Meeting of Human Brain Mapping (Rome, 2019)

Introduction

Obsessive-compulsive disorder (OCD), like other psychiatric disorders, has been related to alterations in the functional connectivity (FC) between brain areas detected with fMRI, supporting the 'patho-connectomics hypothesis', i.e. that the behavioral symptoms characterizing psychiatric disorders may be the expression of an ineffective functional integration at the system level (Stam 2014, Fornito, Zalesky et al. 2015). Nevertheless, previous results were obtained through a static approach, which reduces the whole resting-state timeseries to an average FC matrix (Moreira, Marques et al. 2017). The goal of the present work is to study how these alterations are expressed at the dynamical level by characterizing recurrent FC patterns at the single-TR resolution to gain further insight into the pathophysiology of OCD, a chronic psychiatric disorder affecting 2-3% of the worldwide population.

Methods

Eighty individuals (40 OCD patients and 40 matched healthy controls) underwent an fMRI scanning session during resting-state. Previous history of neuropsychiatric disorder and use of any medication (excluding oral contraceptives) were defined as exclusion criteria for controls. The average BOLD timeseries from the preprocessed resting-state scans were extracted for 116 brain regions using the AAL parcellation scheme. We then used the Leading Eigenvector Dynamics Analysis (LEiDA) approach to assess recurrent FC patterns (Cabral, Vidaurre et al. 2017). Briefly, an instantaneous matrix of BOLD phase coherence was computed for each TR across all subjects, and the corresponding leading eigenvectors were clustered (using k-means with cosine distance) to identify recurrent FC states (represented by each cluster centroid). The probability of occurrence of each recurrent FC state was statistically compared between groups using non-parametric permutation tests.

Results

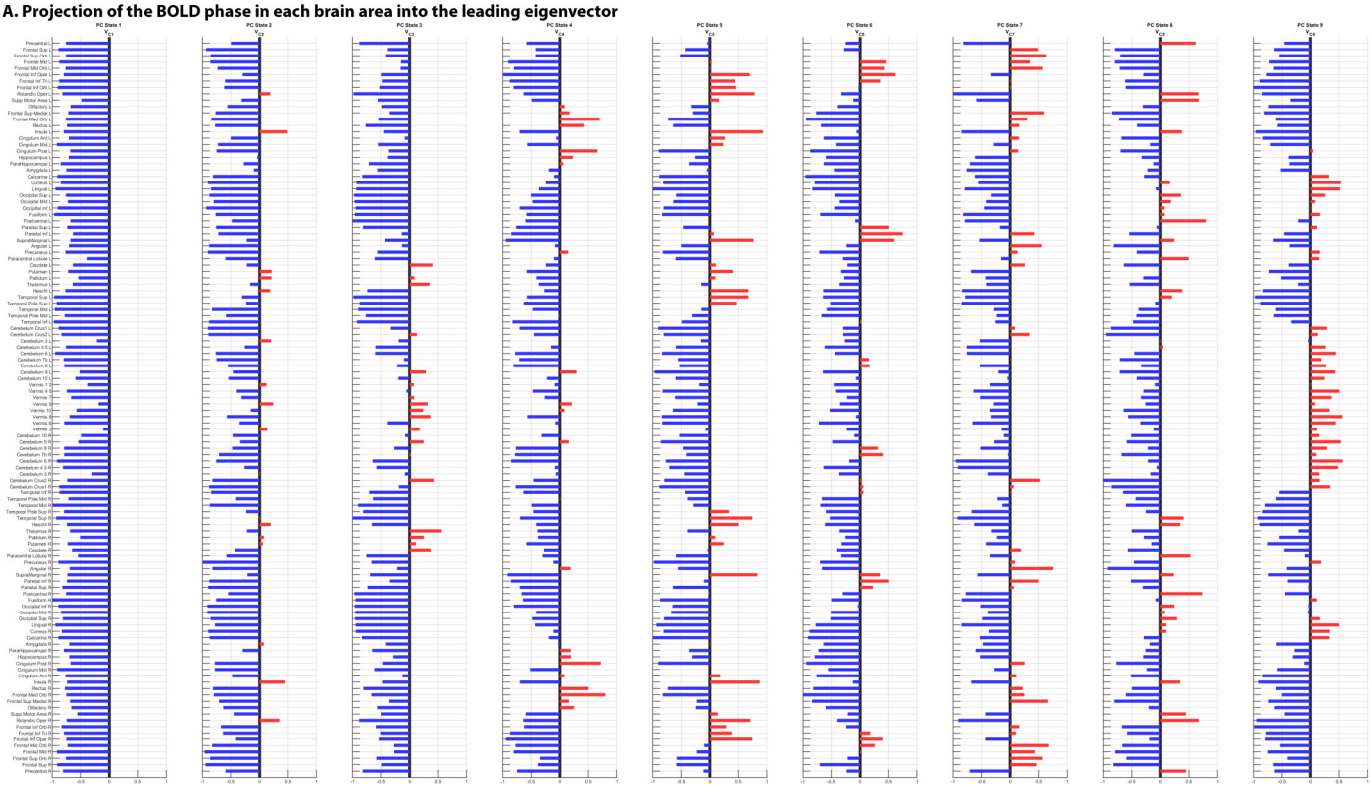
The FC states returned by LEiDA revealed different functional sub-systems (see Figure 1), some of which appearing significantly disrupted in OCD, namely a Limbic-Striatal-Cerebellar network ($p=.0026$) and a Fronto-Parietal-Cerebellar network ($p=.0200$). These FC states are marked by a temporal alignment of BOLD phases between specific brain areas (colored in red in Figure 1), while misaligning from the rest of the brain (colored in blue in Figure 1). Concomitantly, a baseline state of global BOLD coherence was found to occur more frequently in OCD patients in

comparison with healthy controls (p=.0341). Results were robust for a range of partition models ranging from k=7 to k=11, with higher k revealing more fine-grained and less frequent subsystems.

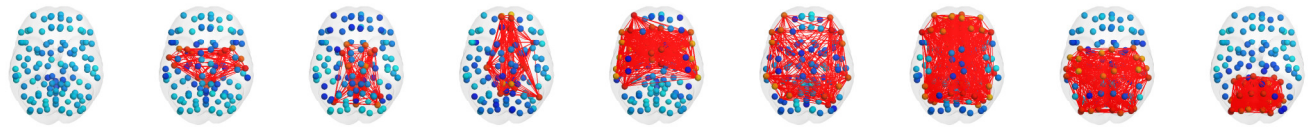
Conclusions

To the best of our knowledge, this is the first study assessing the dynamics of resting-state FC in OCD patients. The use of the LEiDA approach for the characterization of FC patterns in OCD yielded novel findings regarding the dynamic fluctuation between FC states in these individuals, detecting alterations in specific functional subsystems, which may be potentially established as an important biomarker of the disorder and help link the behavioral symptoms of the disease to the underlying network dynamics. An important limitation of this study relies on the fact that most patients were receiving pharmacological treatment. Previous studies have highlighted that the administration of selective serotonin reuptake inhibitor (SSRI) medication contributes to a partial restoring of abnormal FC in these patients (Shin, Jung et al. 2014). As such, future studies may provide further elucidation on this issue, by characterizing the FC dynamics in drug-naïve patients. In addition, given that previous studies have reported that the variety of the regions implicated in the disorder appears to underlie the different OCD phenotypes (Mataix-Cols, do Rosario-Campos et al. 2005), it is still yet to explore how different symptom-related manifestations of the disorder are characterized with respect to FC dynamics.

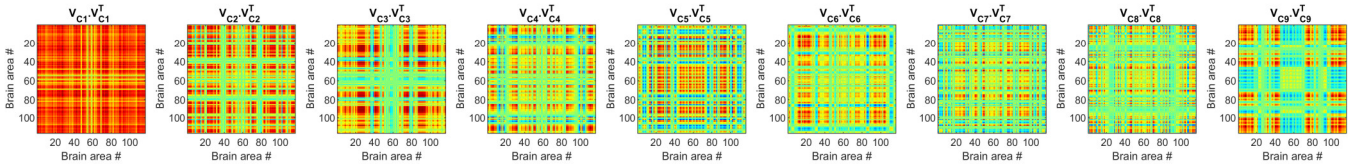
A. Projection of the BOLD phase in each brain area into the leading eigenvector



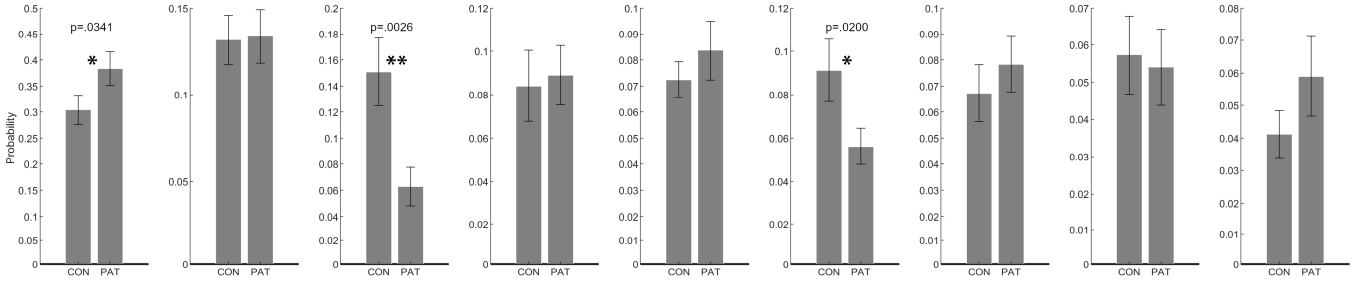
B. Cortical renderings in AAL space of regional contributions to the respective central vector (Vc)



C. Matrix of the outer product of Vc, where positive values are the product of Vc elements with the same sign



D. Probability of occurrence (represented as mean ± standard error of the mean) of each state for each group



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APPENDIX D

Relationship between obsessive compulsive disorder and cortisol: Systematic Review and Meta-analysis

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*first co-authorship

Submitted

Abstract

Altered stress response and consequent elevated levels of circulating glucocorticoids have been found in neuropsychiatric disorders such as depression or anxiety disorders and proposed to also play a role in the pathophysiology of obsessive-compulsive disorder (OCD). Despite the observation that stressful events may precede the disease onset or even exacerbate its symptoms, studies in this field do not always report consistent results regarding the cortisol profile of OCD patients. As such, a systematic review and meta-analysis was developed to clarify this issue. This systematic review and meta-analysis were elaborated according to the PRISMA method. The analytical procedures were implemented using Metafor package in R software. 19 studies were included in the systematic review and 18 were included in the meta-analysis. In qualitative synthesis, 12 studies indicate that cortisol levels are higher in OCD patients than controls, whereas 7 do not reveal significant differences. In quantitative analysis, OCD patients had significantly higher cortisol levels compared to controls ($d=1.079$, $SE=.303$, $p<.001$). For studies using the average of multiple assessments, the standardized coefficient was significantly higher when compared to studies focusing on single measurements. Only the studies performing blood collection in the morning yielded a significant overall effect ($d=.706$, $p=.001$). Both the systematic review and meta-analysis strongly suggest that cortisol levels are significantly higher in OCD patients than healthy individuals.

Keywords: Obsessive-Compulsive Disorder; Cortisol; glucocorticoids; Stress; Hypothalamic-pituitary-adrenal axis

APPENDIX E

10Kin1day: A bottom-up neuroimaging initiative

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Preprint in bioRxiv; with Revisions in Frontiers in Neurology

DOI: https://doi.org/10.1101/509554

Abstract

We organized 10Kin1day, a pop-up scientific event with the goal to bring together neuroimaging groups from around the world to jointly analyze 10,000+ existing MRI connectivity datasets during a 3-day workshop. In this report, we describe the motivation and principles of 10Kin1day, together with a public release of 8,000+ MRI connectome maps of the human brain.

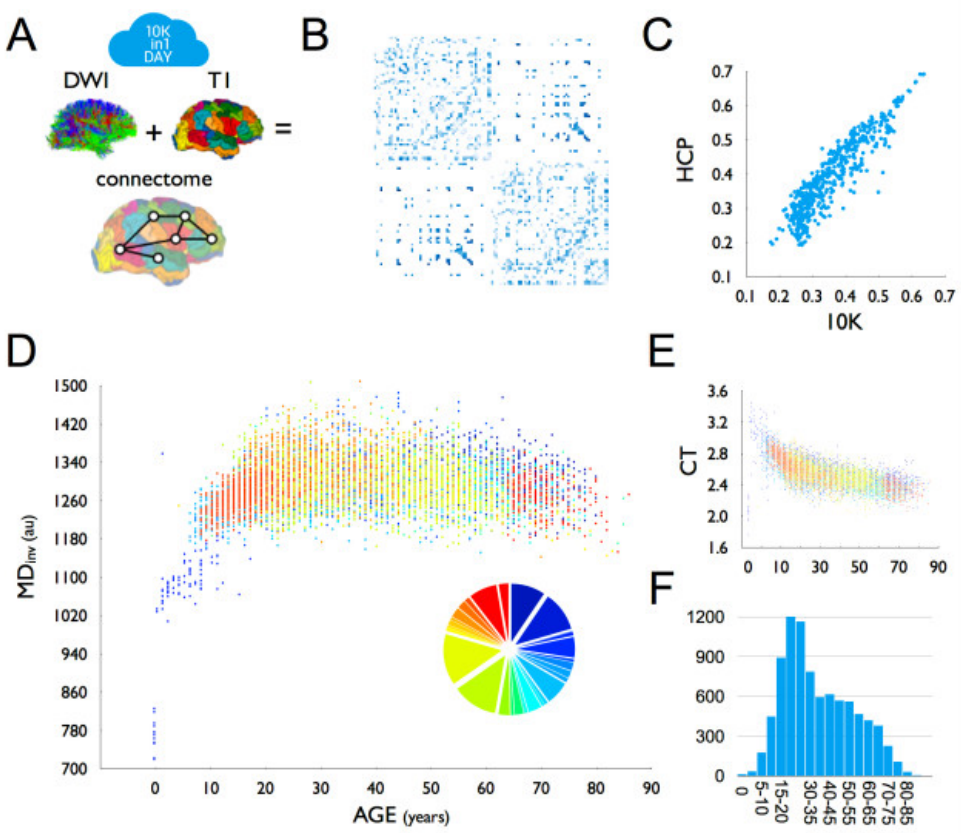

Figure 1. (A) For each dataset, DWI tractography was combined with T1-based parcellation of cerebral brain regions to reconstruct a brain network. (B) Group-averaged (group threshold 33%) FA matrix of the 10K dataset. (C) High overlap (r=0.93) between group-averaged FA values as derived from high-resolution HCP data and the 10K dataset. (D) Relationship between age and average inverse mean diffusivity (MD) across the 10K dataset. Colors indicate the different included datasets. Insert shows a pie diagram of the size of included datasets, color coded to set participation. One dataset (set_634413) was excluded from this plot, showing (across the age span) deviating FA (lower) and MD (higher) values than the other datasets (see methods). Due to the high total n, excluding this dataset did not change the relationship with age. (E) Relationship between age and average cortical thickness (CT). (F) Age distribution of the presented data as in panel E and F. au=arbitrary units. DWI=diffusion weighted imaging. CT=cortical thickness.