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Cingulate Cortex's Volumetry Influence on State and Trait Anxiety

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RESUMO

Introdução: Apesar da elevada prevalência das perturbações de ansiedade, ansiedade é transversal a todos os indivíduos. A ansiedade fisiológica pode ser encarada sob duas formas: Traço e Estado - a primeira corresponde a uma predisposição estável para sentir ansiedade, sendo a segunda um estado emocional transitório. Porém, a compreensão das bases biológicas e do papel das estruturas cerebrais nos traços de personalidade é ainda pouco compreendido. Pela sua relação com fenómenos emocionais e de memória, o córtex do Cíngulo constitui uma potencial região de interesse no estudo da ansiedade.

Objetivos: Compreender a relação entre diferenças estruturais no córtex do Cíngulo e Ansiedade Traço e Estado em indivíduos saudáveis.

Métodos: Estudo observacional transversal com inclusão de 1570 indivíduos, saudáveis, com idades entre 18-35 anos, submetidos a um questionário básico de saúde, seguido de uma RMN estrutural e duas RMN funcionais. Realizaram um conjunto de questionários validados para apurar características cognitivas e comportamentais. Os dados foram compilados e disponibilizados numa base de dados para fim de investigação. Para o presente estudo foram utilizados os dados cedidos relativos à espessura de diferentes regiões do córtex do Cíngulo e à Ansiedade-Traço/Estado apurados através do STAI-Trait/State.

Resultados: Quanto à Ansiedade-Traço, foi demonstrada uma associação com a diminuição da espessura cortical da região rostral do Cíngulo Anterior no hemisfério esquerdo. Quanto à Ansiedade-Estado, foi demonstrada uma associação com o aumento da espessura cortical da região do Cíngulo Posterior no hemisfério direito.

Conclusão: Os resultados sugerem a existência de uma relação entre a estrutura do Córtex do Cíngulo e a Ansiedade-Traço e Estado. Tendo em conta a prevalência das Perturbações de Ansiedade, estes achados podem vir a ser úteis para prever que indivíduos estão em maior risco de desenvolver Perturbações de Ansiedade.

Palavras-chave: Personalidade; Ansiedade; Traço; Estado; Córtex do Cíngulo

ABSTRACT

Introduction: More than the high prevalence of anxiety disorders, all individuals express anxiety. Physiological anxiety can be viewed as two constructs - trait and state anxiety. The first refers to a stable tendency to experience anxiety, with the second being a transient emotional state. Still, the biological basis and the role of brain structure in personality traits remains poorly understood. Given its role in emotion and memory, the cingulate cortex is a potential region of interest in the study of anxiety.

Objectives: The aim of this study is to clarify the influence of structural Cingulate Cortex differences on both trait and state anxiety in healthy individuals

Methods: Cross-sectional observational study, comprised of 1570 individuals, ages 18 to 35, who were asked to complete a basic set of health questionnaires, followed by structural and functional MRI scans. They were asked to complete a battery of behavioral, cognitive and personality assessments. The data was compiled in a database for research purposes. For the present study, it was used the provided data concerning to thickness of several cingulate cortex regions and the State and Trait Anxiety (measured through STAI-Trait/State)

Results: In regard to trait anxiety, the present study results have revealed significant rostral anterior cingulate cortical thickness reduction on the left hemisphere. As for state anxiety, results have demonstrated a significant increased posterior cingulate cortical thickness on the right hemisphere**.**

Conclusion: These findings suggest that might be a relation between the cingulate cortex structure and trait and state anxiety, in healthy individuals. Given the prevalence of anxiety disorders, this may help in predicting who is more vulnerable and who is more likely to develop pathological anxiety.

Key-Words: Personality; Anxiety; Trait; State; Cingulate Cortex

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INTRODUCTION

The term personality refers to a set of enduring qualities of an individual, that are shown in his behavior, thoughts and emotions, in a wide variety of circumstances. (Harrison, Paul; Cowen, Philip; Burns, Tom; Fazel, 2006)

Personality is an important part of the human condition. It affects all of life's parameters, including health. Variations in personality may predispose to psychiatric disorder, by modifying the response to stressful events or affecting the way that patient approaches psychiatric treatment. (Harrison, Paul; Cowen, Philip; Burns, Tom; Fazel, 2006)

Personality models, traits and states

Several models and theories have been proposed to explain the origin of human personality - psychoanalytic, behaviorist, humanistic, social-cognitive, as many others. (Funder, 2001). Despite some controversy, the most widely accepted and the one which gathers more consensus is the trait-theory of personality.

According to Allport (1937), one of the founders of the trait theory, a trait is "a generalized neuropsychic structure (peculiar to the individual), with the capacity to render many stimuli functionally equivalent, and to initiate and guide consistent (equivalent) forms of adaptive and stylistic behavior".

A more contemporary definition is that traits are “endogenous basic tendencies that give rise to show consistent patterns of thoughts, feelings, and actions”; they are distinct from habits – habits are specific learned behaviors, while traits are generalized dispositions, finding expression in a variety of specific acts (McCrae & Costa Jr., 2003).

To some authors, traits are considered the first level of personality, with characteristic adaptations and integrative life narratives being the second and the third levels (McAdams & Pals, 2006).

In summary, traits are enduring individual differences, conditioning a person's behavior, reactions, thoughts, emotions and perceptions of the world. It implies a predisposition to react to many situations in a consistent manner (Endler & Kocovski, 2001).

Although traits are distinct from transient mood or states (Costa Jr. & McCrae, 1998), they may reflect individual differences in the frequency and the intensity in the expression of a certain emotional state (Spielberger, 1972). That is, a personality trait is a conditioning factor on the manifestation of the corresponding state. I.e., the stronger the trait, the more likely the person will experience the corresponding state and have trait-associate behaviors in a variety of situations, and more intense will be that state. (Spielberger, 1972)

Based on the trait theory, several taxonomies for adult personality have emerged.

One of the more consensual is the Five-Factor Model (John & Srivastava, 1999; McCrae & Costa, 1997; Saucier & Srivastava, 2015), which comprehends five categories - *extraversion, neuroticism, conscientiousness, agreeableness* and *openness to experience*. Each one of them represents general dimensions of individual differences (Caspi et al., 2005), and is defined by many more specific traits (Costa Jr. & McCrae, 1998), the lower-order traits (John & Srivastava, 1999). These last are more specific and are composed of more particular responses (Caspi et al., 2005). For example, higher-level neuroticism includes anxiety, vulnerability to stress, guilt-proneness, angriness, insecurity, and others (Caspi et al., 2005).

The biological basis of personality

The biological *perspective* of personality refers to the genetic and physiological factors that influence a person's personality. It tries to understand how personality traits manifest through biology and how the connection between brain, DNA and personality is made (Khormaei & Khatibi, 2016).

Even though personality traits are conditioned by culture, therefore not being exclusively a biological phenomenon (Costa Jr. & McCrae, 1998), they are remarkably stable in adults (McCrae & Costa Jr., 2003).

Studies of behavior genetics support the biological perspective, e.g., identical twins tend to resemble each other even if they grow up in a different environment (Tellegen et al., 1988), and heritability quotients around 50% have been produced for most personality traits (Bouchard et al., 1990; McCrae & Costa Jr., 2003).

The biological *basis* of personality is a theory which claims that anatomical brain structures contribute to personality traits (Khormaei & Khatibi, 2016).

It is known that some anatomical regions of the human brain are extremely important for the individual's behavior: there's a collection of systems in the human brain dedicated to the reasoning and decision, located in ventromedial prefrontal cortices and amygdala (Damasio, 1994); The frontal lobes are important for emotion and attention (Damasio, 1994); The amygdala plays a role in aggression, fear, anger and other emotions as well (Buck, 1999); also, the endocrine system modulates some responses, e.g., testosterone has an influence on sociability and positive affect, as well as on aggressiveness and sexuality (Funder, 2001).

As a contribution to this theory, evidence has been proving that both local brain structure and personality are heritable (Valk et al., 2020).

Furthermore, several studies associating personality traits and the structure of the brain cortex have been emerging. The vast majority has a focus on linking brain volume to the dimensions of the Big-Five (DeYoung et al., 2010; Riccelli et al., 2017; Valk et al., 2020) and phenotypic associations between personality traits and local cortical structure have been proved (Riccelli et al., 2017; Valk et al., 2020)

The findings support the hypothesis that, with mild exceptions, there is a gain of function with the increase of brain tissue volume in predicted brain regions (DeYoung et al., 2010).

As a result, living-day theory suggests that

- Variations in local brain structure and personality can be partly explained by genetics
- Brain structure is an endophenotype linking genes and behavior
- Personality correlates with macro-scale brain structure and function

(Valk et al., 2020)

Anxiety as part of an individual's personality

According to the World Health Organization (WHO), anxiety disorders are the most common mental disorders worldwide, affecting 284 million people in the world.

Beyond anxiety-related disorders, all healthy and non-clinical individuals express and manifest anxiety and anxiety-related feelings across their lives. It is considered as a basic, universally experienced, condition of human existence (Spielberger, 1972).

To Spielberg, anxiety is an emotional state or condition, consisting in feelings of tension and apprehension, associated with an increase in the autonomic nervous system activity (Spielberger, 1972).

According to newer definitions, anxiety also includes worry, negative affect, a feeling of insecurity and an anticipation of a threatening, but vague event (Barlow, 2000; Rachman, 2004)

Anxiety can be viewed as two distinctive constructs - trait anxiety and state anxiety.

Trait anxiety refers to a stable tendency or predisposition to experience and report negative emotions as fear, insecurity, worry and anxiety in a wide range of situations. (Heller, 2013; Reiss, 1997; Spielberger, 1972). Trait anxiety can be included in the neuroticism dimension of the Big-Five-model (Heller, 2013).

State anxiety differs from trait anxiety, because it has a transitory nature: it is a psychophysiological transient state (Leal et al., 2017), which fluctuates over time, in intensity and frequency. State anxiety usually is more pronounced in threatening situations (Spielberger, 1972), and it is an observable response (Reiss, 1997) limited in time.

Despite being two different concepts, trait and state anxiety are correlated in a way that trait anxiety predicts state anxiety responses (Reiss, 1997).

Although this is not a strict rule and exceptions have been verified, in general the higher the trait anxiety, the higher the state anxiety (Horikawa & Yagi, 2012; Leal et al., 2017). Trait anxiety reflects anxiety-proneness (Spielberger, 1966), in other words, a propensity to experience and express anxiety-state reactions.

Personality traits have been shown to be consistently associated with psychological adjustment and well-being (Magee & Biesanz, 2019). Trait anxiety is an important predictor in behavior medicine (Heller, 2013), and it has been associated with an augmented risk for developing anxiety-related disorders (Weger & Sandi, 2018).

Understanding its underlying mechanisms is crucial, and therefore several studies have been made.

Brain structure and anxious personality characteristics: the cingulate cortex

Several brain areas have been targeted to be related to anxiety disorders, such as amygdala, prefrontal cortex (Martin et al., 2009; Patriquin & Mathew, 2017) and cingulate cortex (Madonna et al., 2019). A negative association between cortical thickness of the right rostral anterior cingulate cortex has also been found in populations with social anxiety disorder (Frick et al., 2013).

In healthy individuals, anxiety ratings have been correlated with the gray matter volume of several brain regions, such as prefrontal cortex and *pars opercularis*, dorsolateral PFC bilaterally (Hu & Dolcos, 2017; Spampinato et al., 2009), temporal and parietal regions (Saviola et al., 2020) and the rostral divisions of anterior cingulate cortex (ACC) (Donzuso et al., 2014; Potvin et al., 2015; Saviola et al., 2020; Spampinato et al., 2009)

Cingulate cortex seems to be a particular region of interest in the anxiety phenomenon. It is located around the corpus callosum and it is part of the limbic lobe (Rolls, 2019). Amygdala and hippocampus are structures included in the limbic system as well, and limbic structures' functions and connections are wide across the brain (Rolls, 2019).

Cingulate cortex receives input from many sources and acts modulating the activity in numerous brain regions, thus affecting motor, visceral, endocrine and cognitive responses (Bush et al., 2000). Its anterior and posterior parts seem to have different functions and connections (Rolls, 2015).

Rolls has considered that the anterior cingulate is part of the "emotional limbic system" whereas the posterior cingulate is part of the "memory limbic system" (Rolls, 2015). A few years later, Vogt has proposed a three-part division of the cingulate cortex, referring an "emotional subsystem", which comprises ACC, a "sensorimotor subsystem", which includes the middle region of the cingulate cortex, and a "cognitive spatial map subsystem", for localizing relevant objects and episodes, which comprises PCC (Vogt, 2019).

Back in 1994, Damasio has proposed the existence of a brain region, the Anterior Cingulate Cortex (ACC), where systems associated with emotion/feeling, attention and work memory interact, leading to external action (movement) and internal action (thought animation and reasoning) (Damasio, 1994).

Nowadays, it is known that, because of its privileged position, the anterior cingulate cortex has deep connections with emotion-related areas, such as amygdala, autonomic areas (brainstem, hypothalamus), the hippocamp, and with areas involved with reward processes (orbitofrontal cortex and ventral striatum) (Stevens et al., 2011).

One of the functions of the cingulate cortex is the "action-outcome learning", which is the process of learning the action to perform in order to obtain a reward or avoid a punisher (Rolls, 2019). Furthermore, reward and punishing systems are linked to behavioral activation and inhibition systems, which may correlate to a wide range of emotions, of which anxiety (Buck, 1999).

The anterior cingulate cortex is associated with emotion in a way that, due to its reciprocal connections with emotion-related areas, and because it receives reward and punishment information from orbitofrontal areas, it generates emotional responses, which in turn contributes to behavioral modification (Rolls, 2019). The regulation of these emotional responses is another function attributed to the anterior cingulate cortex (Bush et al., 2000), and that has been corroborated by functional studies in healthy individuals (Giuliani et al., 2011).

The Posterior Cingulate Cortex (PCC) is important in visuospatial processing, by its connections with parietal areas, and in memory, by its strong connectivity with hippocampus (Rolls, 2019).

The role of the cingulate cortex in clinical populations has been well documented in literature. For example, ACC is an important part of the overgeneralization of contextual fear memory, which is associated with anxiety disorders, particularly PTSD (Bian et al., 2019). Functional MRI-studies have revealed a positive correlation between left PCC activation and the exposition to threat-related words (Maddock & Buonocore, 1997). In individuals with Generalized Anxiety Disorder (GAD), Panic Disorder (PD) and Social Anxiety Disorder (SAD) an elevated brain activity in response to threat have been detected in several areas, including the cingulate cortex (Buff et al., 2016).

Attending to the structural point, evidence also suggests that dorsal ACC is smaller in people with certain psychiatric conditions, especially panic disorder (Asami et al., 2008). In addition, a decrease in grey and white matter volumes of the Posterior Cingulate was noticed in adolescents with GAD (Strawn et al., 2013).

On the other hand, the importance of cingulate cortex and its morphometric features (as volume or thickness), in trait and state anxiety, and therefore in personality, remains poorly understood.

Structural studies have also been developed, with evidence pointing to a correlation between anxiety phenotypes in healthy individuals and cingulate cortex structure. However, results were inconsistent, with ones showing negative correlations (Spampinato et al., 2009), others positive correlations (Potvin et al., 2015; Saviola et al., 2020) and others showing no correlation at all (Hu & Dolcos, 2017).

The population used in these studies was also an issue, with samples being too small or having particular features, for example the age.

Additionally, these findings were limited to trait anxiety and to ACC. State anxiety has never been correlated with the brain's structural aspects, with that correlation only being found in functional terms (Saviola et al., 2020).

There is also lack of information regarding the role of PCC's volumetric features in state or trait anxiety. Consequently, more research is required in order to provide strong evidence and comprehension on how brain structure and personality correlates.

Based on the fact that the cingulate cortex is a limbic structure, with major connections and functions across the brain, including emotion and memory, we believe that changes in its structure may conditionate more anxious phenotypes in healthy individuals. We also expect that, taking into account the differences between anterior and posterior cingulate cortex, those structures may contribute differently to the anxiety experience. In more detail, due its role in emotion's modulation and its connections with emotion-related areas, we hypothesize that a volume reduction in the ACC would compromise the suppression of undesired anxiety feelings, and therefore is probably associated with higher anxiety traits. On the other hand, since the PCC is more implicated in memory, we think that an increase in its volume may be responsible for a high quantity of anxiety thoughts, leading to anxiogenic phenotypes.

The aim of this study is to clarify the influence of structural Cingulate Cortex differences on both trait and state anxiety in healthy individuals, in order to provide further evidence on what are the biological basis of personality.

METHODS

Data were provided by the Brain Genomics Superstruct Project of Harvard University and the Massachusetts General Hospital (MGH), (Principal Investigators: Randy Buckner, Joshua Roffman, and Jordan Smoller), with support from the Center for Brain Science Neuroinformatics Research Group, the Athinoula A. Martinos Center for Biomedical Imaging, and the Center for Human Genetic Research. Twenty individual investigators at Harvard Medical Scholl and MGH generously contributed data to the overall project.

Participants

Between 2008 and 2012, young adults (ages 18 to 35) with normal or corrected-to-normal vision were recruited from Boston area universities and colleges, and the surrounding communities.

Many of the participants were informed about the study due to local college recruitment efforts and through studies connected to Harvard University and the Massachusetts General Hospital, but merely a few of the participants were recruited directly from students of Harvard University.

Concomitant participation in a study of normal (non-clinical) brain function or in a case-control study of a clinical population, serving as control participant, were inclusion criteria.

Participants provided written informed consent in accordance with guidelines established by the Partners Health Care Institutional Review Board and the Harvard University Committee on the Use of Human Subjects in Research, and in this dataset are only included those who agreed to data sharing.

The data acquisition has followed a four-step protocol.

First, the individuals were asked to complete a basic set of demographic and health questionnaires - including participants' physical health information, past and present history of psychiatric illness, medication usage and family history of psychiatric illness. These questionnaires were completed just before or directly after the MRI-scan. Then, participants were submitted through a series of structural and functional MRI scans. After and before the scan, a sample of saliva of each participant was obtained. Finally, participants were given instructions in order to complete a web-based battery of behavioral, cognitive and personality assessments.

Self-reported current or past history of Axis I pathology or neurological disorder, current psychotropic medication usage and/or acute physical illness were exclusion criteria. Participants who displayed atypical brain anatomy were excluded as well (n=218).

MRI data acquisition

The MRI-imaging data were collected on matched 3T Tim Trio scanners at Harvard university and Massachusetts General Hospital using the vendor-supplied 12-channel phased-array head coil. Structural data included a high-resolution (1.2mm isotropic) multi-echo MPRAGE (T1-weighted magnetization-prepared gradient-echo image). Multi-echo MPRAGE allows a rapid acquisition when compared to the conventional 1mm MPRAGE (2 minutes vs. 6 minutes), without sacrificing the results, since the morphometric features derived through both of MPRAGE are highly consistent.

The advantages of a faster acquisition are a low participant burden and a reduction of within-scan motion risk - which may compromise the results.

One or two functional MRIs were also acquired, but since they are not used in the present study, the information about the acquisition conditions is omitted.

Images were screened for artifacts, acquisition problems, processing errors and excessive motion, and the data which did not meet the quality criteria were excluded from the dataset.

Therefore, imaging data were converted from DICOM to NIfTI-1 format using mri_convert from FreeSurfer v4.5.0.

The images were also de-identified using a software (mask_face software) which blurs facial anatomy.

Since face distortion of anatomical data can influence morphometric estimates, were included in the dataset the morphometric values for each participant, computed on their original scans.

FreeSurfer v4.5.0 was also used to process the data. It provides automated algorithms for the volumetric segmentation of subcortical structures and estimation of cortical thickness, and it allows users to analyze estimated cortical thickness independent of cortical volume.

Cortical thickness was calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface Estimated intracranial volume was calculated using the strategy detailed in Buckner et al. (Buckner et al., 2004)

(Holmes et al., 2015)

For the present study, we have used the data concerning the cingulate cortical thickness.

Online self-report battery

After the MRI-scans, participants were instructed to undergo an online battery of cognitive, behavioral and personality assessments. To do so, a card with a random de-identified code and two web addresses was provided to each one of the subjects.

The behavioral and personality assessments were hosted on a secure internal server and presented through the LimeSurvey user interface.

Cognitive assessments were presented through an internally developed collection of standard cognitive assessments administered using Adobe Flash from Creative Suite 3.

Participants who failed to initiate or did not complete the entire online assessment, failed to answer more than two questions, or admitted to seeking outside assistance during the batteries were considered non-compliant for the behavioral and personality portion, being excluded from the project. (Holmes et al., 2015)

A lot of behavioral and personality phenotypes were surveyed in the GSP, including State-trait anxiety, NEO Five-factor model of personality, BIS and BAS scale, Barratt, impulsivity scale, as many others.

In the present study, we have used the data concerning the State-trait anxiety inventory (STAI) for adults - measure of trait anxiety and measure of state anxiety.

The STAI was developed by Spielberg and his associates, in order to provide reliable and relatively brief self-report measures of both state anxiety and trait anxiety. Each one is a scale consisting of 20 statements, which inquires the individual about their feelings of tension, nervousness, worry and apprehension and its intensity at a particular moment in time (State anxiety), or about the frequency of those feelings (Trait anxiety) (Spielberg et al., 1971).

All of the data, including data from paper surveys, MRI scans and test batteries were archived and the access was restricted by user authentication and role-based access controls. (Holmes et al., 2015)

Reliability scans

A supplementary dataset was acquired in 69 of the participants, on an independent day, separated less than 6 months from the first one. These additional scans may be useful to estimate test-retest reliability in the future.

Statistical Analysis

Statistical analyses were conducted using STATA Software (version 14.2; StataCorp, Texas, USA) and descriptive statistics were presented as mean ± standard deviation.

To study our hypothesis, we performed two multivariate linear regression models, one with the state-anxiety subscale total score, as the outcome, and other with the trait-anxiety subscale total score. In both models we defined the following variables as predictors: age, sex, hand dominance, years of education and the following structural variables: the right caudal anterior cingulate thickness (mm), the left caudal anterior cingulate thickness (mm), the right rostral anterior cingulate thickness (mm), the left rostral anterior cingulate thickness (mm), the right posterior cingulate thickness (mm), the left posterior cingulate thickness (mm), the right isthmus cingulate thickness (mm) and the left isthmus cingulate thickness (mm).

Measures of effect were expressed as Coefficients (Coef.) and a p-value ≤0.05 was considered statistically significant.

RESULTS

The study included data from 1570 individuals, ages 18 to 35 with a mean age of 21.5±2.89 (92% were under the age of 27 at the date of the scan), 905 participants (57.6%) were female and 92.3% right-handed. The mean years of education were 14.5±1.89.

In regard to trait anxiety, the present study showed that *rostral anterior cingulate cortical thickness reduction* on the **left hemisphere** was a significant predictor of higher scores in the trait-anxiety subscale total score (Coef. -3.24; *p=0.02).*

As for state anxiety, results have demonstrated that *increased posterior cingulate cortical thickness* on the **right hemisphere** was a significant predictor of higher scores in the state-anxiety subscale total score (Coef. 5.38; *p=0.034*).

DISCUSSION

The Anterior Cingulate cortex

To fully comprise the role of the cingulate cortex in anxiety mechanisms, it is important to understand the neural subtracts of anxiety.

Amygdala has been targeted to have a primary role on the neural circuit of anxiety, since its activation has been observed in anxiety and fear studies (Taylor & Whalen, 2015; Vogt, 2018). It is composed of two nuclei: the basolateral, which processes external information and therefore excites the other one, the central nucleus (Robinson et al., 2019). From this one, outputs are sent to other regions, including the limbic cortex, with which maintains reciprocal connections (Martin et al., 2009; Vogt, 2018).

As a matter of fact, the rostral portion of ACC (rACC) is one of the limbic regions more deeply connected to amygdala, having reciprocal connections with other limbic and autonomic areas as well, such as insula (Stevens et al., 2011; Szekely et al., 2017).

Unlike the dorsal ACC, that is implied in cognitive processes, the rACC primary role seems to be the modulation of emotional responses, along with other frontal structures as prefrontal cortex and orbitofrontal cortex (Bush et al., 2000; Stevens et al., 2011; Taylor & Whalen, 2015).

For instance, one of the most interesting roles assigned to the rACC is the top-down control of emotion – the activation of this region leads to a reduction of the activity of several areas, including the amygdala (Etkin et al., 2012; Stevens et al., 2011), which may explain why a reduced rACC cortical thickness is associated to anxiety trait.

Although there isn't a strict relation, in a way that there are many other influences, brain structure and function are well correlated in many areas (Batista-García-Ramó & Fernández-Verdecia, 2018; Messé et al., 2014; Segall et al., 2012), and studies have demonstrated that gray-matter structure is directly associated with functional components (Segall et al., 2012). Moreover, there's a strong evidence-based belief that larger gray-matter leads to an higher function – e.g., the train of certain tasks produces an increase in gray matter structure in associated-brain structures (Boyke et al., 2008) and larger brains show stronger intrinsic brain activity (Qing & Gong, 2016), which can be explain by the fact that the more the neurons, the more the output (DeYoung et al., 2010).

The findings suggest that a reduction on rostral anterior cingulate cortex thickness predicts trait anxiety. Thus, it is reasonable to think that a reduction on the cortical thickness on this region may be expressed by a constant impairment on suppressing amygdala's activity during anxiety experience, as a consequence of a diminished input from the rACC.

Since trait anxiety is a stable characteristic of an individual's personality which expresses as a propensity to experience anxiety-state reactions, a persistent failure on suppressing amygdala would explain the higher vulnerability to those feelings in those individuals.

As matter of fact, evidence has shown that high-anxiety trait individuals have a decreased rACC response, along with an hyperresponsive amygdala, which activity is resistant to extinction (Barrett & Armony, 2009). Other studies found evidence of dysfunctional cortico-amygdala circuitry in anxiety disorders (Kim et al., 2011; Kujawa et al., 2016; Swartz & Monk, 2014) . Also, Kujawa and his colleagues have suggested that a disturbance in top-down regulation of amygdala may be associated with a higher risk of developing anxiety disorders (Kujawa et al., 2016).

The results have shown a significant inverse correlation between trait anxiety and rostral anterior cingulate cortical thickness just on the left hemisphere. The human brain's asymmetry has been well documented and studied across time. Left and right hemispheres are different from both structural, functional and behavioral perspectives (Samara & Tsangaris, 2011), with each hemisphere being specialized in certain cognitive processes (Duboc et al., 2015).

While the left hemisphere is dominant for language and related to logical, rational tasks, such as problem solving, the right hemisphere associates with spatial and visual functions. (Duboc et al., 2015; Samara & Tsangaris, 2011).

When it comes to emotions and emotion processing, the left and right hemispheres display different roles as well. Two main theories have emerged – the right hemisphere theory claims that the right hemisphere appears to be mainly dominant for all kinds of emotions.

From the valence theory perspective, the left hemisphere is mainly dominant for positive emotions while the right hemisphere is dominant for negative emotions, such as fear and aggression. Furthermore, the left hemisphere associates with approach behavior and the right one with avoidance or withdrawal behavior. (Güntürkün et al., 2020).

The two theories are considered not to be mutually exclusive, but complementary, and it is thought that they are referring to two distinct and interacting networks on the brain (Güntürkün et al., 2020). Thus, it is possible that cortical thickness reduction on emotion-related areas, such as rACC, on the left hemisphere, would compromise the experiencing of positive emotions, so that the negative ones would be more prevalent.

Previous findings have demonstrated a correlation between the ACC structure and trait anxiety in healthy individuals.

However, as stated earlier in the introduction section, their results were not consistent with each other. Spampinato *et al.* discoveries were similar to ours, as they reported a negative association between rACC (among other regions) structure and trait anxiety in (Spampinato et al., 2009), with the only difference being the fact that we have used cortical thickness as structural measure, whereas they have used cortical volume. Still, Potvin and his associates have found a larger cortical thickness in trait-anxiety subjects (Potvin et al., 2015), Saviola *et al.* have reported a positive correlation between the ACC gray-matter structure and trait anxiety (Saviola et al., 2020). Donzuso et. Al have positively correlated the ACC volume and trait anxiety being measured with the HARS scales, but that association was not found using the STAI scales (Donzuso et al., 2014).

The Posterior Cingulate Cortex

The results have also shown a positive significant correlation between right posterior cingulate cortical thickness and state anxiety.

The posterior cingulate cortex is one of the most mysterious areas of the human brain, and its function is poorly understood.

It consists of a region with a wide range of connections, both cortical and subcortical, including hippocampus, ventromedial prefrontal cortex and the rACC itself (Leech & Smallwood, 2019).

Interestingly, it is one of the brain regions' with higher metabolism and is included in the Default Mode Network (DMN), along with the adjacent precuneus and lateral parietal cortex, ventromedial prefrontal cortex, the dorsal medial prefrontal cortex, lateral inferior parietal lobes and medial temporal structures (Leech & Sharp, 2014; Raichle, 2015), being also strongly functionally connected with the those DMN regions (Leech & Smallwood, 2019).

A sub-division of the DMN in two connected but distinct networks may be considered, with the PCC being part of the posterior part (Williams, 2016). Besides the DMN connections, the PCC appears to communicate with a wide variety of large-scale brain networks (Leech & Smallwood, 2019), contributing to a broad role in cortical dynamics.

Being part of the DMN, the PCC displays high activity at rest, and that high activity ceases during task performance (Pearson et al., 2011). This leads to PCC implication in emotion, and therefore anxiety – in off-task periods its activity increases, and its capacity to generate introspective thoughts – about past, future, self and social aspects – and retrieve memories emerges. This becomes clear taking into account prior studies, which have documented that, e.g., mind-wandering (Mason et al., 2007) and planning the future (Addis et al., 2007) are associated with higher PCC activity. Actually, emotion regulation, self-inspection and thinking about the past and future are thought to be functions of the DMN (Satpute & Lindquist, 2019; Sylvester et al., 2012). The relation with memory and emotion can be explained taking into account the PCC connections with medial prefrontal cortex and hippocampus. In anxiety, intrusive and constant worrisome thoughts are common, and may be related to long term memory storage (Mathews, 1990).

The PCC plays also a role in arousal and awareness processes, modulates balance between internal and external attentional focus, and it shows high activity during surveillance states (Leech & Sharp, 2014; Vogt, 2019).

In fact, high-level arousal and awareness states are key features of anxiety, together with attention bias towards a possible threat. These factors could explain the role of the PCC in the anxiety process.

Besides that, hyper-alert states can be associated with excessive environment's vigilance, with the role of the PCC in spatial processing, due to its connections with parietal cortical areas, being well described in literature (Rolls, 2019; Vogt, 2019).

The implication of DMN and its nodes in anxiety is not a new discovery, and it has been correlated with several psychiatric disorders, including anxiety disorders (Broyd et al., 2009; Coutinho et al., 2016; Tao et al., 2015). Its function could be compromised at different levels, e.g., at rest, in rest-task transitions, during activity, or due to a dysfunction in anterior-posterior connectivity. Actually, in subjects with anxiety disorders, Coutinho and her associates' work have demonstrated a dissociation between anterior and posterior DMN and in healthy individuals a negative correlation between posterior DMN and anxiety symptoms was found (Coutinho et al., 2016).

On EEG studies, anxiety-trait was also correlated with lower functional connectivity strength of DMN and high-anxiety trait subjects have shown a decrease of connectivity between the right PCC and the right mPFC (Imperatori et al., 2018).

To explain the relationship between the PCC and the anxiety dimensions, we must keep in mind that, primarily, state anxiety should be considered an emotional state, which fluctuates over time in intensity and frequency, being limited in time. The PCC is part of the DMN, which is a set of brain structures with a transient activity as well, being silent during task performance and active during rest. In addition, the PCC has a key role on self and introspective thought, during its high activity period, and it is also important on emotion regulation, memory recall, arousal and awareness states, and visuospatial processes, with all of these playing a part on the complexity of anxiety.

Taking these together, it is possible that an increase in the PCC cortical thickness can lead to a hyperactivity of the system when recruited, explaining the strong correlation with anxiety state.

Although Saviola and his associates' have reported that state anxiety has functional association with DMN posterior regions, including the PCC, a significant correlation between structure and state anxiety wasn't found. Therefore, they have proposed that trait and state anxiety have distinct expressions in the human brain - trait anxiety is a stable predisposition, so it is implemented in structural aspects, and state anxiety is a temporary condition, being correlated with function (Saviola et al., 2020). However, brain structure and function shouldn't be viewed as two independent aspects, since they are directly associated with each other, as previously mentioned (Segall et al., 2012).

Thus, it is reasonable to think that structural changes could be the basis of a functional network. This explains why changes in the PCC structure are predictors of state anxiety, as our results have revealed, and also explains the functional association between state anxiety and the PCC, found in prior studies (Saviola et al., 2020).

The fact that the right hemisphere is dominant for emotions and, above all, for negative emotions such as anxiety, may explain why state and augmented cortical thickness association was only found in the right hemisphere. We believe that the reason is the same as for the trait-anxiety-rACC thickness reduction, as described earlier. Also, prior evidence corroborates these results, since correlation between DMN and trait anxiety using EEG studies was only found for the right hemisphere (Imperatori et al., 2018).

Limitations

The first limitations in this study are related to the sample. For the present study, we have used Brain Genomics Superstruct Project's data, and although it is a large sample, the population is relatively young (ages 18 to 35). That fact may represent a bias, because personality is stable across life, but there is evidence of changes in the cortical thickness and volume with aging (de Chastelaine et al., 2019; Scahill et al., 2003). A decline in cingulate cortex volume with age was also documented (Mann et al., 2011). In addition, and as prior said in Brain Genomics Superstruct Project's paper, since individuals were recruited from Boston and surrounding communities, they have relatively high IQ's. High intelligence has been positively associated to anxiety disorders, but it was correlated with a low degree of worry in healthy individuals (Coplan et al., 2012). Therefore, the IQ bias must be considered when interpreting the results.

Considering the imaging data, a rapid acquisition protocol was used. Although multi-echo MPRAGE morphometric features are consistent with the traditional MPRAGE ones, the faster acquisition may conditionate more artifacts, and no backup sequences were provided (Holmes et al., 2015).

Secondly, trait and state anxiety were estimated through a self-report questionnaire. Evidence suggests that self-reports are as valid as traditional assessments (Germine et al., 2012), but self-reports are naturally modulated by the individuals' own judgment. Besides that, both state and trait were assessed using STAI scales. As discussed earlier, different results were reported depending on the scale used to assess anxiety, whether HARS or STAI (Donzuso et al., 2014), so it would be interesting to replicate the study using a different measure.

Finally, this study has not evaluated the impact of other structures besides cingulate cortex, on trait or state anxiety, and it has only appraised macro-brain structure. Other regions' contribution and the impact of micro-structure or functional changes were not considered. Both personality and human brain networks are complex constructs, and consequently, for future studies, we recommend the assessment of those features in order to have a deeper comprehension on the subject.

CONCLUSIONS AND FUTURE DIRECTIONS

Taken together, our findings suggest that could be a relation between cingulate cortex structure and trait anxiety, in healthy individuals, and provide evidence that, somehow, brain structure and personality traits and states might be related. Cingulate cortex seems to have particular significance in anxiety phenomena.

Given the prevalence of anxiety disorders, this may help in predicting who is more vulnerable and who is more likely to develop pathological anxiety and other mental-health related conditions.

This study provides more evidence on anxiety and its processes, focusing on macro-brain structure. However, further research - on the functional and micro-structural levels, for example - is required to deeply understand this complex phenomenon, and this evidence should be seen as a starting-point for future studies.

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