Structural Brain Correlates of the Externalizing Spectrum in Young Adults

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Abstract—The externalizing spectrum, including traits and behaviors such as aggression, reduced inhibitory control and substance abuse, is associated with altered prefrontal brain morphology. However, the degree to which different manifestations of the externalizing spectrum are associated with distinct or overlapping variations in individual brain morphology is unclear. Here, we therefore used structural magnetic resonance imaging, self-report assessment, and a response inhibition task in a sample of 59 young adults to examine how cortical thickness in the anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and dorsolateral prefrontal cortex (DLPFC) relate to four different manifestations of the externalizing spectrum: disinhibition, callous aggression, substance abuse, and behavioral inhibitory control. Using Bayesian linear regression models controlling for age, gender, and years of education, we found that the different manifestations of the externalizing spectrum were associated with both distinct and overlapping morphology variations. Specifically, both callous aggression and inhibitory control was associated with increased cortical thickness of the OFC, a region involved in reward processing, decision-making, and regulation of anxiety and fear. Both disinhibition and substance abuse were associated with DLPFC thickness, although with opposite association patterns, possibly reflecting processes related to inhibitory control, working memory and attention. Moreover, disinhibition, but not callous aggression or substance abuse, was associated with behavioral inhibitory control. Our results provide further support for the link between externalizing behaviors and prefrontal brain morphology, while identifying distinct prefrontal areas associated with different clinically relevant manifestations. These findings may help guide further research aimed at developing novel treatment and intervention strategies for externalizing behaviors and disorders. © 2021 The Author (s). Published by Elsevier Ltd on behalf of IBRO. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Key words: externalizing, disinhibition, callousness, aggression, substance abuse, cortical thickness.

INTRODUCTION

The externalizing spectrum is a broad, dimensional construct, encompassing normal-range traits and behaviors such as sensation seeking, aggression, and reduced inhibitory control as well as severe psychopathological syndromes such as childhood conduct disorder, adult antisocial personality disorder, and substance use disorders (Kendler et al., 2003; Krueger et al., 2005; Patrick et al., 2012). Importantly, different manifestations of the externalizing spectrum may arise due to distinct etiological factors (Krueger et al., 2002). Clarifying the neurobiological underpinnings of these different manifestations, using a combination of neuroscientific, self-report, and experimental methods, may offer a more precise understanding of their respective etiology and clinical relevance, and may help guide research towards novel targets for treatment and intervention (Patrick et al., 2012; Cuthbert, 2014; Perkins et al., 2020).

While the externalizing spectrum is diverse, it appears to form a coherent, hierarchical structure (Krueger et al., 2007). The Externalizing Spectrum Inventory-Brief Form (ESI-BF; Patrick et al., 2013), a shortened version of
Externalizing Spectrum Inventory (Krueger et al., 2007), allows for efficient, dimensional self-report assessment of three moderately correlated subfactors — General Disinhibition, Callous-Aggression, and Substance Abuse — each indexing different manifestations of the externalizing spectrum. To date, however, no study has investigated how these ESI-BF subfactors relate to cortical morphology, raising the question of the degree to which the ESI-BF subfactors reflect the underlying neurobiology. Furthermore, traits and behaviors along the externalizing spectrum have also been robustly associated with impaired inhibitory control (Bohlin et al., 2012; Castellanos-Ryan et al., 2014), possibly due to a shared impaired inhibitory control (Venables et al., 2018), no study has, to the best of our knowledge, explored associations between all of the ESI-BF subfactors and inhibitory control. Thus, studies linking the ESI-BF subfactors to inhibitory control are called for.

A wealth of neuroimaging studies has shown robust associations between traits and behaviors along the externalizing spectrum and alterations in the brain’s structure and function, primarily in frontal regions (Yang et al., 2008; Yang and Raine, 2009). For instance, at the severe end of the externalizing spectrum, antisocial and psychopathic individuals have demonstrated reductions in prefrontal gray matter volume ranging from 10% to 20% compared to controls (Raine et al., 2000; Yang et al., 2005). A more recent review, however, suggests that the disinhibitory and antisocial aspects of psychopathy may be associated with increased prefrontal and striatal gray matter volume (Korponay and Koenigs, 2020). Three frontal brain regions — the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), and the dorsolateral prefrontal cortex (DLPFC) — have emerged as particularly interesting in research on externalizing traits and behaviors (Yang and Raine, 2009). These regions have been robustly associated with specific behavioral measures such as inhibitory control (Whelan et al., 2012; Oldrati et al., 2016), moral decision-making and antisocial behavior (Yang and Raine, 2009; Glenn and Raine, 2014; Rosell and Siever, 2015; Raine, 2019), as well as with substance use and addiction (Ersche et al., 2013). In addition, research has found evidence of reduced prefrontal thickness both in conduct-disordered and aggressive children and in antisocial and psychopathic adults (Yang et al., 2010; Fahim et al., 2011; Ly et al., 2012; Ameis et al., 2014; Jiang et al., 2016). Still, it remains unclear if specific manifestations of the externalizing spectrum are differentially related to variations in cortical morphology within the same individuals.

Here, we asked whether different manifestations of the externalizing spectrum, measured using the ESI-BF and a Go/NoGo task assessing response inhibition, are differentially associated with overlapping or distinct alterations in individual brain structure. To do so, we used structural magnetic resonance imaging (MRI) and examined associations between individual variability in cortical morphology, Go/NoGo task performance, and the three subfactors of the ESI-BF. Specifically, based on previous research (Young et al., 2009; Yang et al., 2010; Fahim et al., 2011; Ly et al., 2012; Ameis et al., 2014; Jiang et al., 2016), we expected that the ESI-BF subfactors would be negatively associated with both Go/NoGo task performance and with cortical thickness in the ACC, OFC, and DLPFC. Finally, we also conducted exploratory whole-brain analyses to examine any further associations between externalizing and cortical thickness.

**EXPERIMENTAL PROCEDURES**

**Ethical statement**

The study was conducted in accordance with the Declaration of Helsinki, and was approved by the Regional Ethics Committee in Gothenburg, Sweden (DNR 538-18). All participation was voluntary and based on informed, written consent.

**Participants and procedures**

Community volunteers were recruited using ads on social media, and interested participants, who did not meet exclusion criteria for MRI (pregnancy, claustrophobia, battery-powered implants, and foreign metal objects sensitive to magnetic fields) were invited to MRI scanning. A total of 59 participants (39 females, 19 males, 1 non-binary) were available for MRI scanning, and thus included in the current study. The response inhibition task was completed on-site either immediately before or after MRI scanning, and self-report assessments were collected using online questionnaires. Participation, including online questionnaires, took approximately two hours, with four movie tickets (worth ~$40) as compensation.

**Self-report assessment**

The ESI-BF (Patrick et al., 2013) is a self-report instrument consisting of 160 items, rated from 0 (Not true at all) to 3 (Completely true). A subset of items may be summed to three moderately correlated subfactor that index different manifestations of the externalizing spectrum. The General Disinhibition subfactor (ESI-BF_DIS) consists of 20 items related to disinhibition, including problematic impulsivity, irresponsibility, impatience, and proneness to boredom, with possible scores ranging from 0 to 60. The Callous-Aggression subfactor (ESI-BF_AGG) consists of 19 items related to deficient empathy, relational aggression, destructiveness, excitement seeking, and dishonesty, with possible scores ranging from 0 to 57. The Substance Abuse subfactor (ESI-BF_SUB) includes 18 items related to recreational and problematic use of alcohol, marijuana, and other substances, with possible scores ranging from 0 to 54. Internal reliability was assessed using both Cronbach’s alpha and McDonald’s Omega (McNeish, 2018). All subfactors showed high internal reliability, with Cronbach’s alpha = 0.87, 0.92, 0.89 and McDonald’s Omega total = 0.90, 0.94, 0.92, for the ESI-BF_DIS, ESI-BF_AGG, and ESI-BF_SUB, respectively.
Task-based response inhibition

Response inhibition was assessed using a Go/NoGo task based on previous work (Kiehl et al., 2000), implemented using Presentation (Neurobehavioral Systems Inc.), with all source code available online at the Open Science Framework (https://osf.io/m4vd/; DOI https://doi.org/10.17605/OSF.IO/M4V9D). Participants were seated comfortably approximately 60 cm from a 14-inch laptop in a quiet and secluded room. Oral and on-screen instructions told them to quickly and accurately respond by pressing the left mouse button every time a Go stimulus (a white letter “X”) appeared, and to withhold their response when a NoGo stimulus (a white letter “K”) appeared. Both Go and NoGo stimuli were presented for 250 milliseconds against a black background, with a fixation point located at the center of the screen presented between trials. The inter-stimulus interval was pseudorandomly distributed between 1000 and 3000 milliseconds at 500 ms increments. Participants first completed 10 practice trials requiring at least 50% correct responses in order to proceed. If less than 50% were correct, 10 new trials began, and so on, until the threshold for correct response was met. Then followed a total of 326 trials, divided into two blocks of 163 trials each, with rest in between. A total of 274 Go trials (84%) and 52 NoGo trials (16%) were used, in order to establish a prepotency to respond, thus making it more difficult to inhibit responses. We used the ratio between the number of successful inhibitions on NoGo trials and the total number of trials as a measure of inhibitory control (i.e., NoGo accuracy; NoGoACC). Higher NoGoACC means that the participant committed fewer commission errors, also known as “false alarms.”

MRI data acquisition

Structural brain scans were collected using a Philips Gyroscan 3 T Achieva, software release 3.2 with a 32 channelSENSE head coil (Philips, Eindhoven, The Netherlands). T1-weighted scans (3D T1-TFE) were acquired with the following parameters: flip angle 8°, TE = 4.0 ms, TR = 8.4 ms, SENSE factor 2.7, TFE factor 240, 170 sagittal slices with scan resolution 1.0 x 1.0 x 1.0 mm³.

Image processing and surface-based morphometry

Structural brain images were processed with the Computational Anatomy Toolbox, version r1615 (CAT12; Gaser and Dahnke, 2016) for SPM12, version 6225 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) using MATLAB, version R2020a (Mathworks, Natick, MA, USA). The automated procedure includes denoising and bias correction, tissue segmentation, and spatial normalization to MNI coordinate space using Geodesic Shooting (Ashburner and Friston, 2011). The CAT12 toolbox rated all data as having good (N = 58) or satisfactory (N = 1) image quality. Surface data was then resampled and smoothed using the high-resolution Freesurfer mesh and a 12 mm FWHM smoothing kernel, and cortical thickness was estimated using the projection-based thickness method (Dahnke et al., 2013). For a priori region of interest analyses, thickness estimates were parcellated into thirty-four regions based on gyral and sulcal structure of the Desikan-Killiany atlas (Desikan et al., 2006), from which cortical thickness values were extracted. Based on previous research (Yang et al., 2010; Fahim et al., 2011; Ly et al., 2012; Ameis et al., 2014; Jiang et al., 2016), five regions of interest were selected for each hemisphere: the caudal and rostral ACC, the medial and lateral OFC, and the rostral middle frontal gyrus, which corresponds to the DLPFC (Fig. 1).

Statistical analysis of self-reports, task-based response inhibition, and region of interest data

A robust, fully Bayesian approach, with weakly informative priors centered around zero providing moderate regularization (Gelman et al., 2017) was used for all statistical analysis of self-report, task-based response inhibition, and region of interest data. Analyses were carried out using R, version 4.0.0 (R Core Team, 2020), and all R code is available online at the Open Science Framework (https://osf.io/m4v9d, DOI https://doi.org/10.17605/OSF.IO/M4V9D). Statistical models were specified using the R package brms (Bürkner, 2017), interfacing R with the Stan programming language (Carpenter et al., 2017). Numerical variables were standardized prior to modelling, and we used 8 chains of 4000 Markov chain Monte Carlo iterations, with 2000 warmup samples.

Zero-order correlations between performance on the response inhibition task and ESI-BF subfactors were examined using linear models with a Student’s T distribution (Lange et al., 1989) and a correlation matrix drawn from a LKJ(2) prior (Lewandowski et al., 2009). To assess the association between cortical thickness and different manifestations of the externalizing spectrum, we used linear regression models (one for each hemisphere and dependent variable) modelled with the Student’s T distribution (Lange et al., 1989). The three ESI-BF subfactors and response inhibition performance were entered as dependent variables, with measures of cortical thickness as predictors, and we controlled for the effect of age, gender, and years of education.

We report median estimates of standardized regression coefficients ($\beta$) and correlation coefficients ($\rho$) along with 90% credible intervals (CrIs), presented within square brackets. Following previous examples of how to quantify uncertainties in everyday language (Mastrandrea et al., 2011), a 90% CrI may be interpreted such that there is a 90% probability — or very likely — that the parameter estimate falls within its range. For figures, we also plot the 66% CrI, which may be interpreted as a “likely region.” In order to facilitate interpretation of results for readers unfamiliar with the Bayesian framework, we use $P_D$ to denote the probability of direction, which may be interpreted as the probability that the parameter estimate is different from zero (Makovski et al., 2019). The $P_D$ ranges from 50% to 100%, and has a 1:1 correspondence to the frequentist p-value, such that $p_{two-tailed} = 2 \times (1 - (P_D/100))$. 
Whole-brain statistical analysis

We conducted whole-brain analyses using the second-level general linear model approach implemented in SPM12. Five linear regression models were computed to assess the association between cortical thickness and ESI-BF DIS, ESI-BF AGG, ESI-BF SUB, and NoGo ACC, with age, gender, and years of education as covariates. We used peak family-wise error (FWE) correction thresholded at $p_{FWE} < 0.05$ to address multiple comparisons.

RESULTS

Participants

Participants’ average age was 23 years (SD = 3, range = 18–32) and with an average of 14 years of education (SD = 2, range = 10–21). Fifteen participants (25%) reported a current or previous psychiatric disorder, the most frequent being anxiety-related disorders ($N = 9$; 15%) and depression ($N = 9$; 15%), although with considerable overlap. Twenty-three participants (39%) reported some form of current medication, the most frequent being antidepressants ($N = 8$; 14%), non-benzodiazepine anxiolytics ($N = 3$; 5%), and psychostimulants ($N = 2$; 3%). No participant reported any current or previous neurological disorder. A descriptive overview of self-reported externalizing traits and behaviors, task-based response inhibition, and cortical thickness is presented in Table 1.

Correlations between self-report assessments and task-based response inhibition

ESI-BF DIS was robustly and negatively correlated with NoGo ACC ($\rho = -0.19 [-0.39, 0.03]$, $P_D = 93\%$), but no robust correlations between NoGoACC and ESI-BF AGG ($\rho = 0.08 [-0.13, 0.29]$, $P_D = 74\%$) or ESI-BF SUB ($\rho = -0.05 [-0.27, 0.17]$, $P_D = 64\%$) were observed. ESI-BF DIS showed robust, positive correlations with ESI-BF AGG ($\rho = 0.51 [0.32, 0.66]$, $P_D = 100\%$) and ESI-BF SUB ($\rho = 0.52 [0.34, 0.66]$, $P_D = 100\%$). ESI-BF AGG and ESI-BF SUB showed a robust and positive, although smaller correlation ($\rho = 0.26 [0.04, 0.45]$, $P_D = 98\%$).

Regional cortical thickness analyses

After controlling for the effects of age, gender, and years of education, higher scores on the ESI-BF DIS were associated with increased lateral OFC thickness ($\beta = 0.20 [-0.07, 0.47]$, $P_D = 69\%$) and with decreased right DLPFC thickness ($\beta = -0.16 [-0.43, 0.11]$, $P_D = 84\%$). Higher ESI-BF AGG scores were associated with increased thickness in the right ($\beta = 0.25 [0.00, 0.52]$, $P_D = 95\%$) and, although with a small effect, left medial OFC ($\beta = 0.13 [-0.11, 0.37]$, $P_D = 83\%$), as well as the right caudal ACC ($\beta = 0.17 [-0.05, 0.38]$, $P_D = 90\%$). Higher scores on the ESI-BF SUB were associated with increased thickness in the right DLPFC ($\beta = 0.18 [-0.09, 0.46]$, $P_D = 87\%$), and higher NoGo ACC was associated with reduced thickness in the left ($\beta = -0.34 [-0.61, -0.06]$, $P_D = 98\%$) and right ($\beta = -0.29 [-0.56, -0.01]$, $P_D = 96\%$) lateral OFC, with increased thickness in the right medial OFC ($\beta = 0.34 [0.06, 0.63]$, $P_D = 98\%$), and, with a small effect, right rostral ACC ($\beta = 0.15 [-0.10, 0.39]$, $P_D = 98\%$).
**Whole-brain cortical thickness analyses**

No vertices survived at $P_{FWE} \leq 0.05$. For exploratory purposes, the results were assessed at an uncorrected threshold ($P_{uncorrected} \leq 0.001$). At this more lenient threshold, effects were observed in multiple regions across both hemispheres, including the orbitofrontal cortex, posterior cingulate, insula, as well as temporal and parietal areas (Fig. 3; details are available in Tables S1–S4 in the Supplementary material).

**DISCUSSION**

Combining structural MRI, a comprehensive self-report assessment, and a well-validated response inhibition task in a sample of young adults, we investigated whether different manifestations of the externalizing spectrum are associated with individual variability in cortical thickness in overlapping or distinct prefrontal cortex areas. Our results suggest that different manifestations of the externalizing spectrum are associated with both overlapping and distinct prefrontal brain regions: Both callous aggression and inhibitory control were associated with cortical thickness of the OFC, whereas disinhibition and substance abuse showed opposite associations with DLPFC thickness. Moreover, disinhibition, but not callous aggression or substance abuse, was correlated with behavioral inhibitory control.

**Associations between self-report assessments and task-based response inhibition**

Our results showed that ESI-BF$_{DIS}$ scores were robustly associated with worse performance on the Go/NoGo task, in line with previous research suggesting that impaired response inhibition may be a valuable endophenotype for disinhibitory psychopathology (Young et al., 2009). Indeed, the ESI-BF$_{DIS}$ contains no drug- or aggression-related items, and thus captures the propensity towards deficient impulse control that lies at the core of the externalizing spectrum (Krueger and South, 2009). In addition, neither callous-aggressive tendencies nor substance abuse were associated with performance on the response inhibition task in the current study. Notably, ESI-BF$_{DIS}$ scores could explain 25% of the variance in these subfactors, indicating that they may primarily tap traits and behaviors along the externalizing spectrum beyond the core, disinhibitory features.

The association between ACC thickness and externalizing traits and behaviors

ACC thickness was associated with better performance on the response inhibition task, supporting previously observed links between task-based response inhibition and the ACC (Braver et al., 2001; Menon et al., 2001; Albert et al., 2012; Hegarty et al., 2012). Specifically, we found that a thicker right rostral ACC was moderately associated with better response inhibition performance. The rostral ACC is extensively activated following incorrect responses in the Go/NoGo task, and appears to be an integral part of the brain’s error monitoring system (Kiehl et al., 2000). Increased thickness in this region may therefore promote learning to avoid incorrect responses, resulting in better performance on the Go/NoGo task. In addition, increased right caudal ACC thickness was moderately associated with higher ESI-BF$_{AGG}$ scores. Previous research has shown that increased cortical thickness in the right caudal ACC may be related to increased neural activity in the same region during the Go/NoGo task (Hegarty et al., 2012), suggesting that increased right caudal ACC thickness could indeed result in an increased capacity for inhibitory control. Still, neither disinhibition nor performance on the response inhibition task was robustly associated with right caudal ACC thickness in the current study (although both associations were in the expected, i.e. negative, direction). The caudal ACC, as defined by the Desikan-Killiany atlas (Desikan et al., 2006), corresponds to a region often referred to as the dorsal ACC or, alternatively, the (anterior) midcingulate cortex (Heilbronner and Hayden, 2016; Vogt,

**Table 2.** Results from robust linear regressions showing the association between cortical thickness and different manifestations of the externalizing spectrum in regions of interest ($N = 59$)

| Region      | General Disinhibition | Callous-Aggression | Substance Abuse | NoGo accuracy |
|-------------|-----------------------|--------------------|----------------|---------------|
|             | $\beta$ [90% CrI]     | $P_D$              | $\beta$ [90% CrI] | $P_D$         | $\beta$ [90% CrI] | $P_D$ |
| **Left**    |                       |                    |                |               |
| Caudal ACC  | $-0.11 [-0.37, 0.14]$ | 76%                | $0.06 [-0.18, 0.36]$ | 67%           | $0.07 [-0.18, 0.32]$ | 67%           | $0.13 [-0.12, 0.37]$ | 80%           |
| Rostral ACC | $-0.01 [-0.24, 0.23]$ | 52%                | $0.00 [-0.21, 0.21]$ | 51%           | $0.11 [-0.13, 0.36]$ | 78%           | $0.07 [-0.17, 0.32]$ | 70%           |
| Lateral OFC | $-0.02 [-0.29, 0.26]$ | 54%                | $-0.11 [-0.35, 0.14]$ | 76%           | $-0.02 [-0.30, 0.25]$ | 55%           | $-0.34 [-0.61, -0.06]$ | 98%           |
| Medial OFC  | $-0.02 [-0.28, 0.24]$ | 55%                | $0.13 [-0.11, 0.37]$ | 83%           | $-0.11 [-0.38, 0.15]$ | 76%           | $0.07 [-0.18, 0.32]$ | 69%           |
| DLPFC       | $0.15 [-0.14, 0.43]$  | 80%                | $0.09 [-0.18, 0.35]$ | 71%           | $0.15 [-0.14, 0.45]$ | 80%           | $0.09 [-0.20, 0.37]$ | 69%           |
| **Right**   |                       |                    |                |               |
| Caudal ACC  | $-0.09 [-0.34, 0.17]$ | 72%                | $0.17 [-0.05, 0.38]$ | 90%           | $-0.09 [-0.34, 0.16]$ | 72%           | $-0.12 [-0.37, 0.13]$ | 80%           |
| Rostral ACC | $-0.02 [-0.27, 0.23]$ | 56%                | $0.06 [-0.18, 0.28]$ | 67%           | $0.01 [-0.24, 0.26]$ | 52%           | $0.15 [-0.10, 0.39]$ | 84%           |
| Lateral OFC | $0.20 [-0.07, 0.47]$  | 89%                | $0.04 [-0.20, 0.30]$ | 61%           | $0.11 [-0.18, 0.39]$ | 73%           | $-0.20 [-0.56, -0.01]$ | 96%           |
| Medial OFC  | $0.13 [-0.15, 0.41]$  | 78%                | $0.25 [0.00, 0.52]$ | 95%           | $-0.09 [-0.39, 0.21]$ | 69%           | $0.34 [0.06, 0.63]$ | 98%           |
| DLPFC       | $-0.16 [-0.43, 0.11]$ | 84%                | $-0.11 [-0.38, 0.14]$ | 75%           | $0.18 [-0.09, 0.46]$ | 87%           | $-0.07 [-0.35, 0.21]$ | 65%           |

Note. ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; DLPFC, dorsolateral prefrontal cortex; CrI, credible interval. Standardized coefficients represent posterior medians and are controlled for age, gender, and years of education. Brain regions are based on the Desikan-Killiany atlas (Desikan et al., 2006).
Although its precise functions are still debated, this region forms a nexus of emotional, cognitive, and motor control, including processes related to the evaluation and monitoring of errors, conflicts, and rewards (Ebitz and Hayden, 2016; Heilbronner and Hayden, 2016). While speculative, one possible explanation is that the association between increased thickness of the right caudal ACC and higher levels of callous aggression stem from increased capacity for evaluation and monitoring of rewards, resulting in an increased likelihood of causing harm to others, if it is perceived as rewarding to do so.

### The association between OFC thickness and externalizing traits and behaviors

Contrary to our expectations, increased thickness of the right lateral OFC was moderately associated with higher scores on the ESI-BF _dis_ and, bilaterally, robustly associated with worse performance on the Go/NoGo task. The OFC is a complex region, although one important function of the OFC is to derive the value of a potential reward in order to guide behavior towards a specific outcome (Wallis, 2007). Recently, increased attention has been given to the distinct functions of OFC subdivisions. Specifically, the medial OFC appears to be involved in the anticipation of a reward, whereas the lateral OFC is involved in the processing of punishment, non-reward (i.e., when the expected reward was not obtained), and suppression of previously rewarded responses (Rolls, 2019). The lateral OFC is also believed to be active during the making of risky choices, perhaps due to overriding a wish to avoid unwanted or punished behavior (Elliott, 2000), and there is mounting evidence of increased OFC activity during reward processing in impulsive-antisocial individuals (Murray et al., 2018). Thus, increased thickness in this region may facilitate the kind of risky, reckless behavior that is captured by the ESI-BF _dis_ subfactor. Along these lines, it is also possible that a propensity towards risky decision-making could explain why increased cortical thickness of the bilateral lateral OFC robustly predicted worse Go/NoGo performance in the current study. Furthermore, since the lateral OFC is functionally connected to the DLPFC (Kahnt et al., 2012), future research may want to combine measures of both functional and structural connectivity to explore this further explore whether structural alterations in the lateral OFC region also affect functions supported by the DLPFC.

A thicker bilateral medial OFC was robustly associated with higher ESI-BF _agg_ scores, and, in the right hemisphere, robustly associated with better performance on the response inhibition task. The ESI-BF _agg_ subfactor — reflecting aggressive, destructive, and antagonistic tendencies — serves as a link between general disinhibitory tendencies and the core, affective-interpersonal features of psychopathy, as evidenced by its association with both affective-interpersonal and impulsive-antisocial psychopathic traits (Venables and Patrick, 2012; Patrick et al., 2013). In this sense, our findings align with studies reporting increased gray matter volume of the right medial (Gao et al., 2020) and bilateral

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**Fig. 2.** Standardized regression coefficients, controlling for the effect of age, gender, and years of education, showing the association between different manifestations of the externalizing spectrum and cortical thickness in regions of interest. Dots represent posterior medians, thick bars represent 66% credible intervals, and narrow bars represent 90% credible intervals. Light and dark green colors indicate coefficients with an estimated probability of > 80% and > 90% or higher of being different from zero, respectively. Brain regions are based on the Desikan-Killiany atlas (Desikan et al., 2006).
medial OFC (De Brito et al., 2009; Fairchild et al., 2013) in children and adolescents with conduct problems and high degrees of callous-unemotional traits, compared to healthy controls. Our results also agree with prior research showing a positive association between both impulsive-antisocial and overall psychopathic severity and right medial OFC volume (Korponay et al., 2017b), as well as with prior work demonstrating a positive association between both impulsive-antisocial as well as interpersonal-affective psychopathic traits and left medial OFC volume (Cope et al., 2012). However, previous research has shown that the medial OFC is activated during the Go/NoGo task (Hom et al., 2003), in line with our findings, but we observed no robust correlation between response inhibition performance and ESI-BF\textsubscript{agg} scores in the current study. A possible conclusion is that while a thicker right medial OFC may indeed facilitate improved response inhibition performance, the association between ESI-BF\textsubscript{agg} and cortical thickness in the right medial OFC could be related to other mechanisms, not directly tied to inhibitory control. In fact, and in line with our correlation results, the ESI-BF\textsubscript{agg} subfactor does reflect several non-disinhibitory aspects of the externalizing spectrum, with items tapping callousness, lack of empathy, and indifference to, or even finding pleasure in, harming others. The observed positive relationship between right medial OFC thickness and callous-aggressive tendencies could reflect a link between reward sensitivity and the likelihood of causing harm to others, particularly since increased activity in brain regions associated with reward may cause psychopathic individuals to derive pleasure from harming others (Glenn and Raine, 2009).

In addition to reward-related processing, the medial OFC is also involved in the regulation of anxiety and fear (Milad and Rauch, 2007; Hiser and Koenigs, 2018). Cortical thickness in the right medial OFC has been negatively correlated with trait anxiety, perhaps due to decreased flexibility in controlling fear along with increased susceptibility to emotional trauma (Kühn et al., 2011). It is possible that the opposite — that is, increased thickness in the right medial OFC — may result in reduced anxiety and an increased ability to control fear and withstand emotional trauma. Indeed, the ESI-BF\textsubscript{agg} subfactor captures a tolerance or even preference for risk and danger (Patrick et al., 2013), and low anxiety and fearlessness has been associated with both interpersonal-affective and impulsive-antisocial features of psychopathy (Neumann et al., 2013). Furthermore, research has shown that fearless children are at high risk of developing callous-unemotional traits (Goffin et al., 2018). Thus, increased right medial OFC thickness may be a neurobiological correlate of reduced anxiety and/or increased fearlessness that results in callous-aggressive tendencies. Interestingly, a more detailed investigation of the fear construct challenges the notion of reduced subjective experience of fear in psychopathic individuals, suggesting instead that psychopathy is associated with deficiencies in threat detection and responsivity (Hoppenbrouwers et al., 2016). Still, research suggests that the right medial OFC is recruited when anticipating an unpredictable threat, thereby allowing fear responses to be regulated (Kirlic et al., 2017). Taken together, the current study observed a complex pattern of OFC morphology in relation to disinhibition, callous aggression, and response inhibition performance. While we have offered some potential explanations for these findings, it is clear that further research is required to elucidate the role of OFC morphology in different manifestations of the externalizing spectrum.

**The association between DLPFC thickness and externalizing traits and behaviors**

A thinner right DLPFC was moderately associated with higher scores on the ESI-BF\textsubscript{DIS}. This finding corresponds well with research showing that the DPLFC...
is involved in inhibitory control (Zhang and Iwaki, 2019), including during the Go/NoGo task (Menon et al., 2001), and is corroborated by our own findings of a robust, negative association between ESI-BF_{DIS} scores and performance on the Go/NoGo task. In addition, transcranial direct stimulation over the right DLPFC has been shown to improve inhibitory control (Beeli et al., 2008), further establishing a link between the right DLPFC and disinhibition. The role of the DLPFC in response inhibition tasks may not be related to inhibitory control per se, however, but rather to associated processes involving working memory and attention (Craud and Boulinguez, 2013). The right DLPFC is involved in representing task instructions and manipulating information in working memory (Courtney, 2004), two processes crucial for optimal Go/NoGo performance. Since the current study did not include any tasks related to working memory or attention, however, we cannot explore this further, although future research may want to consider investigating behavioral tasks that cover a broader range of cognitive functions.

Unexpectedly, we found that a thicker right DLPFC was moderately associated with higher ESI-BF_{SUB} scores. Although there are reports of increased cortical thickness across several frontal and parietal regions in adolescents with heavy substance use compared to controls with more limited use (Jacobus et al., 2015), previous research mainly associate substance abuse with a thinner DLPFC (Durazzo et al., 2011; Jacobus et al., 2016). Notwithstanding our divergent findings, the above-mentioned role of the DLPFC in working memory may offer a potential explanation for this surprising finding. Goldstein and Volkow (2011) have proposed a model wherein enhanced DLPFC activity is involved in forming drug-related working memories, based in part on evidence of increased DLPFC neural activity, along with associated increases in craving and severity of drug use, in response to drug-related cues. In keeping with this model, it is possible that increased thickness of the DLPFC facilitates the forming of drug-related memories, which then results in increased self-reported substance use. Indeed, the moderate correlation between the two subfactors in the current study does leave room for a differential association with DLPFC morphology that warrants further exploration in future research. Still, even though both the medial OFC and the caudal ACC are key regions in the model put forward by (Goldstein and Volkow, 2011), and even though structural abnormalities in the ACC and OFC are robustly related to substance use (Ersche et al., 2013), we observed no association between the ESI-BF_{SUB} and thickness in these regions. Furthermore, previous studies have found reduced left DLPFC volume in antisocial and substance dependent adolescents, along with a negative association between DLPFC volume and impulsivity and substance use severity (Dalwani et al., 2011). However, Dalwani et al. (2011) and the studies included in the meta-analysis by Ersche et al. (2013) examined patients at the extreme end of the substance abuse spectrum, and it is possible that individual variation in cortical morphology may be too subtle to detect in a sample of community volunteers. Thus, a different population and, preferably, a larger sample size, along with using additional measures of substance use, could have rendered different and more robust findings.

**Considering our findings in relation to previous research**

Several additional results deviate from previous research. Specifically, while we found increased right caudal ACC and bilateral medial OFC thickness in relation to callous aggression, and increased lateral OFC thickness in relation to disinhibition, several studies have documented reduced thickness and volume in multiple regions, including the OFC and ACC, in aggressive, antisocial, and psychopathic samples (Tiihonen et al., 2008; Yang et al., 2010; Fahim et al., 2011; Ly et al., 2012; Ameis et al., 2014; Jiang et al., 2016; Rogers and De Brito, 2016; Sebastian et al., 2016), and at least two studies on children and adolescents have found negative associations between aggression and right ACC thickness (Ducharme et al., 2011) and volume (Boes et al., 2008). Furthermore, we found no robust association between ACC thickness and ESI-BF_{DIS} scores, in contrast to previous research showing associations between reduced bilateral caudal ACC thickness and increased impulsivity and sensation seeking (Holmes et al., 2016).

Similarly, it must be mentioned that research on impulsivity — a construct closely related to disinhibition — has primarily shown negative associations with OFC volume and thickness. The Barratt Impulsiveness Scale (BIS-11; Patton et al., 1995) is perhaps the most widely used self-report measure of impulsivity (Stanford et al., 2009), and consists of three subscales (Attentional Impulsivity, Motor Impulsivity, and Non-Planning Impulsivity) in addition to a total score (Patton et al., 1995). The three subscales as well as the total score have shown moderate to strong associations (r 0.43–0.59) with the ESI-BF_{DIS} subfactor in healthy samples (Byrne et al., 2016; Sokić and Ljubin-Golub, 2019; Saneecka, 2020), suggesting that the two instruments may tap similar disinhibitory tendencies. Despite this, previous research in healthy adults has observed negative associations between right middle OFC gray matter volume and BIS-11 Non-Planning Impulsivity score (Matsuo et al., 2009), and negative associations between right medial OFC gray matter volume and BIS-11 total, Motor Impulsivity, and Non-Planning Impulsivity scores (Korponay et al., 2017a). Furthermore, Schilling et al. (2012) found that BIS-11 total score was associated with decreased cortical thickness in the left OFC, whereas BIS-11 Motor Impulsivity and Non-Planning Impulsivity scores were associated with decreased cortical thickness in the right OFC.

Differences in study populations (e.g., offenders vs. community participants) and design (e.g., categorical vs. dimensional approaches) may be one source of discrepancy between the current and previous studies. Another possibility is the varying age of study participants (e.g., children vs. adults), since both cortical thickness and volume follow non-linear trajectories across the lifespan (Ducharme et al., 2015; Fjell et al., 2015). Finally, the use of different structural measures may affect results. Gray matter volume is a function of both cortical thickness and surface area, and these reflect
distinct and uncorrelated cellular and genetic mechanisms, with different developmental trajectories (Chen et al., 2013; Lyall et al., 2015). In light of this, directly comparing volumetric findings and research on cortical thickness may not be viable. To date, relatively few studies have investigated cortical thickness in relation to traits and behaviors along the externalizing spectrum, and future research should consider studying both cortical thickness and surface area in addition to volume. In sum, it is clear that more research is required in order to elucidate the role of ACC, OFC, and DLPFC structure and function in disinhibited, impulsive, and callous-aggressive traits and behaviors. Incorporating other measures, such as the BIS-11, may also yield further insights.

Finally, 15% of the sample reported current or previous anxiety-related disorders, and 15% reported current or previous depression (with considerable overlap between the two). Although the prevalence rates observed in the current study are in line with Swedish epidemiological research (Johansson et al., 2013), and thus representative of community volunteers, a brief mention of the structural correlates of these disorders is warranted. Recent work suggests that the development of internalizing (e.g., anxiety, depression) and externalizing symptoms may be associated with distinct neurodevelopmental paths in late childhood, and that, for instance, reduced thinning of the medial OFC is associated with increased internalizing symptoms (Whittle et al., 2020). In addition, meta-analytic research has found evidence of gray matter volume reductions in both the ACC, DLPFC, and OFC in individuals with major depressive disorder (Bora et al., 2012; Lai, 2013; Wise et al., 2017). On the other hand, research on adults has observed increased gray matter volume primarily in basal ganglia structures among patients with generalized anxiety disorder (Hilbert et al., 2015). Furthermore, a recent study on children and young adults (aged 7–21 years) found that both depressive symptoms and impulsivity were associated with reduced cortical thickness in the ventromedial prefrontal cortex/medial OFC, but that only depressive symptoms remained significant when analyzed jointly with impulsivity (Merz et al., 2018). It seems possible, therefore, that the regions investigated in the current study may be involved both in internalizing and externalizing. While we have focused on different manifestations of the externalizing spectrum in the current study, future research may want to explore how different manifestations of externalizing relate to different manifestations of internalizing, in terms of their respective relationship with cortical morphology.

Strengths and limitations

The current study has some methodological strengths. First, we employed a comprehensive self-report instrument that facilitates dimensional research on externalizing behavior, in broad agreement with emerging frameworks such as the Research Domain Criteria (Carcone and Ruocco, 2017) and the Hierarchical Taxonomy of Psychopathology (HTOP; Kotov et al., 2017). Second, we complemented the self-report instrument with a well-validated response inhibition task. Third, the dimensional approach of the current study offers greater reliability and more substantial correlations with neurobiological measures compared to traditional, categorical approaches (Perkins et al., 2020). Fourth, when possible, we have used robust Bayesian statistical models, and have avoided discussing our findings based solely on frequentist interpretations of statistical significance (Wasserstein et al., 2019). Finally, we used a surface-based cortical thickness approach that complements previous research on gray matter volume.

Notwithstanding these strengths, several limitations should be mentioned. First, we limited the study to three a priori selected regions, while other frontal, temporal, and parietal regions may also be involved in traits and behaviors along the externalizing spectrum (Hyatt et al., 2012; Wallace et al., 2014; Yang et al., 2015). Likewise, the use of the Desikan-Killiany atlas (Desikan et al., 2006) may also have limited our results, since other atlases differ in their parcellation of the brain. Second, single tasks, such as the Go/NoGo, are relatively impure in the sense that they may not fully capture the variance associated with different manifestations of the externalizing spectrum. Using multiple tasks to assess response inhibition is therefore recommended (Young et al., 2009). Third, while we have speculated on the role of the brain’s reward system in relation to our findings, we did not include a reward-related experimental task, which limits our interpretations. Fourth, with a total of 40 a priori estimates reported, some readers may be concerned about correcting for multiple comparisons. It is important to note that correcting for multiple comparisons may not be directly applicable in Bayesian settings, although it is an active research area, though unfortunately with no clear consensus about how and when, if at all, such correction is necessary (Gelman and Tuerlinckx, 2000; Gelman et al., 2012; Sjölander and Vansteelandt, 2019). Nevertheless, all Bayesian models used weakly informative priors centered around zero, which does provide moderate regularization by pushing all estimates towards zero, which at least ameliorates the issue of multiple comparisons. Finally, it is important to note that the Swedish translation of the ESI-BF has yet to be properly validated, and a recent study on the Dutch translation failed to fully confirm the factor structure of the ESI-BF (Soe-Agnie et al., 2020), which should prompt caution in the interpretation of our findings.

In sum, and to the best of our knowledge, this is the first study to examine the link between externalizing behaviors as measured using the ESI-BF and brain structure, and one of few that investigates task-based response inhibition performance in relation to cortical thickness in young adults. Two findings emerged as particularly robust: Both callous aggression and better inhibitory control were associated with cortical thickness of the OFC, a region involved in reward processing, decision-making, and regulation of anxiety and fear. Disinhibition and substance abuse showed opposite associations with DLPFC thickness, possibly reflecting processes related to inhibitory control, working memory, and attention. With several limitations in mind, these findings may be important for further research aimed at...
finding novel targets for treatment and intervention (Patrick et al., 2012; Perkins et al., 2020).

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APPENDIX A. SUPPLEMENTARY DATA

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