Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis

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Abstract

Voxel-based morphometry (VBM) studies of gray matter volume (GMV) in psychopathy have produced inconsistent results and few have been replicated. Therefore, to clarify GMV abnormalities associated with psychopathy as operationalized by Hare (2003), we conducted a meta-analysis of VBM studies using both categorical and dimensional analyses. We identified 7 studies eligible for the categorical meta-analysis (136 men with psychopathy vs 150 male controls) and 11 studies (N=519) eligible for dimensional meta-regressions. First, we used Seed-based *d* Mapping with Permutation of Subject Images for voxel-based meta-analyses. Statistical parametric maps (SPMs) of GMV were available for 4 (57%) of the studies included in the categorical meta-analysis and for 5 (45%) of the studies included in the dimensional meta-regression analyses, with peak coordinates available for the remaining studies. Second, we used meta-data of a large-scale neuroimaging database to provide an objective and quantitative account of psychological processes attributed to the brain regions we identified in our group meta-analysis and meta-regressions. Men with psychopathy exhibited reliable GMV abnormalities circumscribed to the left hemisphere in the dorsolateral prefrontal cortex and the medial orbitofrontal cortex. Total psychopathy scores, Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures. We discuss how decreased GMV in those regions likely account for the impairments in the emotion, cognition, action and perception domains seen in the disorder.

Key words: Psychopathy; gray matter volume; voxel-based morphometry; meta-analysis; signed differential mapping.

General Scientific Summary: This review shows that psychopathy and specific dimensions of the disorder are associated with gray matter volume decreases in two prefrontal regions, as

well as a wider set of regions including midline, temporal, parietal, occipital and subcortical structures.

Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis

Psychopathy is a personality disorder that manifests as a syndrome characterized by a constellation of affective (e.g., lack of empathy and remorse, and callousness), interpersonal (e.g., grandiosity, glibness, superficial charm, and the manipulation of others) and behavioral characteristics (e.g., impulsivity, early behavioral problems/delinquency and criminal versatility) (Hare & Neumann, 2008). In comparison to individuals without psychopathy, those with psychopathy start offending younger (Wong, 1985), exhibit more instrumental aggression (Porter & Woodworth, 2006), are more often convicted or charged for violent offences (Hare & McPherson, 1984; Kosson, Lorenz, & Newman, 2006), and are more likely to reoffend following release (Hemphill, Hare, & Wong, 1998). Consistent with those behavioral features, individuals with psychopathy exhibit emotional (Kosson et al., 2006) and cognitive impairments (Mitchell et al., 2006), as well as abnormal neural responses (Deming & Koenigs, 2020; Poeppl et al., 2018; Verona, Sprague, & Sadeh, 2012) that have been related to socio-affective dysfunction and poor decision-making (e.g., (Hosking et al., 2017).

These behavioral, experimental and functional neuroimaging data, together with neuropsychological studies examining the above domains (Blair, Mitchell, & Blair, 2005), suggest that the clinical presentation of psychopathy and its functional impairments might be underpinned by structural abnormalities in a network of cortical and subcortical regions (Blair & Zhang, 2020; Pera-Guardiola et al., 2016). Consistent with this view, Pera-Guardiola and colleagues recently showed in individuals with psychopathy that lower grey matter volume (GMV) in the prefrontal cortex (orbitofrontal, inferior frontal, and dorsomedial), somatosensory cortex, anterior insula, cingulate cortex, and cerebellum were related to poorer recognition of facial expressions of emotions (Pera-Guardiola et al., 2016); a reliable impairments in psychopathy (Dawel, O'Kearney, McKone, & Palermo, 2012).

A small number of structural MRI studies have used automated and unbiased methods, such as voxel-based morphometry (VBM), to characterize whole-brain and regional GMV in individuals with psychopathy. Intriguingly, no overall differences between individuals with psychopathy and controls have been reported for total intracranial volume (Contreras-Rodríguez et al., 2015; Pera-Guardiola et al., 2016; Tiihonen et al., 2008), or total GMV (Contreras-Rodríguez et al., 2015; Pera-Guardiola et al., 2016; Schiffer et al., 2011), but a number of studies did not report this information (Bertsch et al., 2013; de Oliveira-Souza et al., 2008; Gregory et al., 2012; Müeller et al., 2008). Those studies, however, have reported that individuals with psychopathy are characterised by reduced GMV across several cortical and subcortical regions (for reviews, see Johanson,Vaurio, Tiihonen, & Lähteenvuo, 2019; Pujol, Harrison, Contreras-Rodriguez, & Cardoner, 2019). Cortical regions include frontal (medial/lateral orbital, superior, dorsal, medial, polar, and lateral subregions), temporal (superior, middle, inferior, and fusiform), parietal (inferior lobule), occipital, as well as anterior/posterior cingulate and insular cortices. Subcortical regions include the amygdala, hippocampus, and striatal regions, notably the caudate and putamen. We note, however, that one study has also reported increased GMV in the caudate (Schiffer et al., 2011) and the amygdala (Schiffer et al., 2011) to be associated with higher psychopathy scores. In sum, this VBM literature shows that there are marked inconsistencies across studies in the foci of reduced GMV, which encompass the four lobes of the brain and several subcortical structures.

Possible causes for inconsistent findings and lack of replication are variations in data analytic approaches and sample characteristics within and across studies. For example, the relatively small sample size for most, but not all (Gregory et al., 2012), studies could have resulted in low statistical power and increased risk of both type I and II errors (Button et al., 2013). Furthermore, psychopathy as defined by the PCL-R is underpinned by two correlated

factors, with Factor 1 indexing the interpersonal and affective features of the disorder, while Factor 2 includes items assessing impulsivity and a chronic antisocial lifestyle (Hare & Neumann, 2008). However, several studies adopting a group-level design (i.e., individuals with psychopathy vs those without psychopathy) (Bertsch et al., 2013; Gregory et al., 2012; Tiihonen et al., 2008) have failed to examine the association between factors of psychopathy and GMV abnormalities, with those that have reporting divergent patterns of associations with cortical GMV (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Pera-Guardiola et al., 2016; Schiffer et al., 2011). Finally, it must be noted that two recent meta-analyses of fMRI data on psychopathy either did not (Poeppl et al., 2018) or could not (Deming & Koenigs, 2020) examine the association between the two factors of psychopathy and brain response, which is an important limitation (Latzman, Patrick, & Lilienfeld, 2020).

Consistent with the evidence that psychopathy lies on a continuum (Edens, Marcus, Lilienfeld, & Poythress, 2006; Guay, Ruscio, Knight, & Hare, 2007), five VBM studies (the two studies by Korpornay and colleagues used the same sample) have used dimensional analyses (i.e., regression or correlations analyses) to examine the association between the degree/severity of overall psychopathy (and its Factors) scores as measured by the PCL-R and GMV (Cope et al., 2012; Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012; Korponay et al., 2017a; Korponay et al., 2017b; Leutgeb et al., 2015). Two of those studies found that *Total psychopathy* scores were negatively correlated with GMV in temporal and limbic/paralimbic regions (Cope et al., 2012; Ermer et al., 2012), but divergent correlations were reported for prefrontal and subcortical regions (e.g., caudate, thalamus). In three of those studies (Cope et al., 2012; Ermer et al., 2012; Korponay et al., 2017b), PCL-R *Factors 1 and 2* scores were shown, respectively, to correlate negatively and positively with GMV, notably in the prefrontal cortex, suggesting that the two factors of psychopathy might be associated with different pathophysiological processes. However, there were also notable

inconsistent findings across the five studies, notably in the prefrontal cortex, thus supporting the need for dimensional analyses examining the association between psychopathy factors scores and GMV across those studies.

In this context, a meta-analysis of the VBM data in relation to psychopathy would constitute a valuable theoretical advance in this field by providing a better understanding of the nature and topography of the structural brain abnormalities *reliably* associated with psychopathy. Those data, in conjunction with the results of the two recent fMRI meta-analyses (Deming & Koenigs, 2020; Poeppl et al., 2018), could in turn inform, and possibly refine, the two neurobiological models of the disorder (Blair, 2013; Kiehl, 2006). The Integrated Emotion Systems (Blair, 2013) identifies the amygdala, striatum, and ventromedial/orbito prefrontal cortex as the core regions implicated in psychopathy whereas the Paralimbic Hypothesis (Kiehl, 2006) includes a more widespread set of closely related regions (i.e., amygdala, orbitofrontal cortex, cingulate cortex, parahippocampal area, and insula), which share similar cytoarchitectonic features in terms of neuronal type, structure and density. While both models identify the amygdala and the orbitofrontal cortex as a key regions, so far the VBM evidence is mixed. Furthermore, because most of the studies include small samples, both type I and II errors could detrimentally influence those models.

Therefore, given the inconsistent results in this literature, we did not formulate specific hypotheses and conducted meta-analyses on all published whole-brain VBM studies in psychopathy using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). Only whole-brain VBM studies were included to ensure that results were not biased or restricted to a priori regions of interest (Radua et al., 2012). To increase the accuracy and sensitivity of our analyses, we included the original SPMs from four (57%) of the studies included in our categorical meta-analysis (Radua et al., 2012). Diagnostic tests (publications bias and heterogeneity analyses) were

performed to assess the robustness of our findings. Furthermore, we also conducted dimensional meta-regressions to examine the association between Total psychopathy, Factor 1 and 2 scores, and GMV across 11 studies including 519 participants. Finally, consistent with a recent meta-analysis of fMRI studies on psychopathy (Poeppl et al., 2018), in order to provide an objective and quantitative account of psychological processes attributed to the brain regions we identified in our group meta-analysis and meta-regressions, we statistically assessed their psychological mental functions. This was achieved by linking psychological processes to the identified regions using meta-data of a large-scale neuroimaging database of healthy participants. This objective process of combining functional localisation and characterisation provides an observer-independent link between pathophysiology and psychopathology.

Method

Search and Study Selection

A literature search of The PubMed, ScienceDirect, Scopus and Web-of-Science databases for VBM studies published in English language between 2008 – the year of the first three VBM studies in psychopathy (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Tiihonen et al., 2008) – and February 2020 was carried out by SADB and DM independently. The study selection procedure is summarized in Figure 1. Titles, abstracts, citations and reference lists of the outputted studies were assessed to determine relevance and to identify additional studies for inclusion. Studies were included in main meta-analysis if they (1) focused on psychopathy as defined by the PCL-R (or its screening version, the PCL:SV (Hart, Cox, & Hare, 1995)), (2) compared individuals with psychopathy to controls, and (3) used VBM to examine GMV. Participants were considered as individuals with psychopathy if they had diagnosis of psychopathy established via the PCL-R using the established cutoff scores in North America (i.e., 30) and Europe (i.e., 25). For the PCL:SV the cutoff score was

18. Studies were excluded (see Supplemental Table 1) from the main meta-analysis if they failed (1) to use VBM, (2) to report a voxel-wise comparison between individuals with psychopathy and controls for GMV, (3) did not report whole-brain results, (4) used different significance or extent thresholds when reporting results across the whole brain, (5) included duplicated data sets, and (6) did not provide peak coordinates or SPMs after contact with the authors.

Studies were included in the meta-regression analyses if they (1) had a measure of psychopathy such as the PCL-R or PCL:SV, and (2) examined GMV using VBM. Exclusion criteria for the meta-regression analyses were the same as for the main meta-analysis, except for criterion 2). We contacted the corresponding authors to request the original SPMs (at height and extent thresholds of $p<.001$ uncorrected and 0 voxel, respectively, as recommended by (Albajes-Eizagirre, Solanes, Fullana, et al., 2019) and to obtain additional details where necessary).

Comparison of regional gray matter volumes

Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI; v.6.21) software (http://www.sdmproject.com/software/) (Albajes-Eizagirre, Solanes, Vieta, et al., 2019) was used for voxel-based meta-analyses, comparing GMV differences in individuals with psychopathy and controls. SDM-PSI enables original SPMs and peak coordinates to be combined with established meta-analytical statistics (Methods S1 and Figure S1) (Albajes-Eizagirre, Solanes, Vieta, et al., 2019). SPMs used in this meta-analysis refer to group-level results for the comparison between individuals with psychopathy and controls. Both positive and negative effects are reconstructed within the same map, thus preventing a particular voxel from appearing in opposite directions. These negative effects are also included in the meta-analyses (Radua et al., 2012). The inclusion of the SPMs increases the statistical power of the meta-analysis and provides a more accurate representation of the results (Radua et al., 2012).

SPMs for the group-wise comparison were obtained for four (57%) of the seven included studies (Table 1), while for three studies (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Tiihonen et al., 2008) peak coordinates of significant group differences between individuals with psychopathy and controls were used.

All the studies, but one (Müeller et al., 2008), controlled for total intracranial volume (Bertsch et al., 2013; Contreras-Rodríguez et al., 2015; de Oliveira-Souza et al., 2008; Tiihonen et al., 2008), total brain volume (grey matter + white matter) (Korponay et al., 2017b), or total GMV either via their statistical analyses (as covariate of no interest; (Contreras-Rodríguez et al., 2015)) or via their pre-processing pipeline (performed via a non-linear deformation on the normalized segmented grey matter images; (Gregory et al., 2012; Schiffer et al., 2011)), so our meta-analysis's results reflect *regional* group differences as commonly reported in VBM studies (Ridgway et al., 2008).

Results are reported corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) family-wise-error (FWE) correction ($p<.05$) to optimize sensitivity while adequately controlling for Type 1 errors (Albajes-Eizagirre, Solanes, Fullana, et al., 2019). Meta-analysis Of Observational Studies in Epidemiology (MOOSE; Table S5) (Stroup et al., 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Table S6) (Liberati et al., 2009) guidelines were followed.

Diagnostics: Publication bias and heterogeneity

Several diagnostics were examined to aid interpretation of the results. First, to assess whether the available literature is biased toward excluding studies with non-significant results, an Orwin's fail safe-analysis *N* (Orwin, 1983) was performed. Second, funnel plots were produced, and associated Excess Significance Tests (Ioannidis & Trikalinos, 2007) were computed. Third, to assess the heterogeneity among the results of the included studies, the I^2 index was calculated with values of .25, .50, .75 indicating low, medium, and high

heterogeneity, respectively (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006).

Meta-Regressions

Linear meta-regression analyses were used to examine the influence of: (i) psychopathy Total score, and psychopathy (ii) Factor 1 and (iii) Factor 2 scores on GMV. Because the assessment tools used to measure psychopathy differed across studies (Tables 1 and 2), PCL-R and PCL:SV Total and Factor 1 and 2 scores were converted to Percent of Maximum Possible (POMP) scores (Fischer & Milfont, 2010), consistent with our approach in a previous meta-analysis (Rogers & De Brito, 2016) (Methods S2 and Table S2).

SPMs for the meta-regression analyses were obtained for five (45%) of the 11 studies included (Table S2). For the remaining six studies, original SPMs were not available, so peak coordinates taken from correlational analyses with psychopathy Total and Factor 1 and 2 scores were used. The meta-regressions used a stricter threshold to control for false-positives (p<0.017, Bonferroni-corrected [.05/3] for the 3 meta-regressions described above) (Radua et al., 2012). For the meta-regressions the permutations (N=50 imputations) were conducted at the study-level exploring differences in the value of the moderators of interest (psychopathy Total, Factor 1 and 2 scores) at this level using the Freedman-Lane method for optimal statistical performance (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) and predicting values within the observed range of the computed variable (i.e. from -1 to 1)(Albajes-Eizagirre, Solanes, Vieta, et al., 2019; Radua et al., 2012). The output from the meta-regression linear models represents the amount of grey matter change per unit increase in moderators of interest (Total, Factor 1 and 2 scores).

Functional Characterization

The regions identified by our meta-analysis were then functionally characterized based on metadata from the BrainMap database (Laird et al., 2009, Laird et al., 2011, & Fox

et al., 2002) using reverse inference, which tests the probability of a mental process being present, given knowledge that a particular brain region is activated. This approach involves the identification of all experiments that activate the particular region of interest in healthy participants, and the analyses of the experimental meta-data describing the experimental settings that were employed in those experiments. This allows statistical inference on the type of tasks that evoke activation in the particular region of interest. BrainMap codes tasks along two dimensions. Behavioral domains (BD) describe the cognitive processes probed by an experiment and comprises the main categories action, cognition, emotion, interoception, and perception (http://www.brainmap.org/taxonomy/behaviors.html). Paradigm classes (PC) describe the specific task used. In the reverse inference approach, the functional profile was determined by identifying the most probable taxonomic label, given activation in a particular region of interest. This probability, [P(Task|Activation], can be derived from [P(Activation|Task], as well as P(Task) and P(Activation) using Bayes' rule. A chi-squared test was used to test significance [p<0.05, corrected for multiple comparisons using FDR].

Results

Included Studies and Sample Characteristics

Twenty-four potential studies were identified for inclusion in the meta-analysis. Seventeen studies were excluded from the main meta-analysis based on inclusion/exclusion criteria (Figure 1 and Supplement Table 1). Seven eligible studies (Table 1) included a direct comparison of GMV between individuals with psychopathy (N=136 M age=33.64 years; SD=8.59; range=18–64 years) and controls (N=150 M age=32.51 years; SD=9.02; range=18–61 years) and were thus included in the group meta-analysis. All the participants across the seven studies were males with three of those studies including prisoners. For the meta-regressions, 11 studies (Table S2) were included, seven of which were part of group meta-analysis described above. Those 11 studies included 519 participants (M age= 34.5 years;

SD=8.9; range=18–64 years), out of which 30 were females from one study (Cope et al., 2012). Five of the 11 studies included prisoners. Finally, nine of the 11 studies used the PCL-R to assess psychopathy (*Total score*: M=24.8; SD=5.6; range=2.1–40; *Factor 1*: M=8.9; SD=3.0; range=0–16; *Factor 2*: M=13.4; SD=3.4; range=2.2–18), while the remaining two used the PCL:SV (*Total score*: M=14.5; SD=3.6; range=5-24; *Factor 1*: M=7.1; SD=2.6; range=2-12; *Factor 2*: M=7.4; SD=1.7; range=1–12).

Figure 1 about here

Table 1 about here

Individuals with psychopathy vs. controls: Gray matter differences

Individuals with psychopathy had decreased GMV in the left dorsolateral prefrontal and the left medial orbitofrontal cortices when compared to controls (Table 2; Figure 2).

Figure 2 about here

Table 2 about here

Publications Bias and Heterogeneity

Using Rosenthal (1979)'s threshold of unpublished studies exceeding $5n + 10$, where n represents the number of studies included in the meta-analysis, the Orwin's fail safe-analysis N (Orwin, 1983) for the direct comparison of GMV between individuals with psychopathy and controls indicated that a potential publication bias was unlikely, as 169 studies showing no effect would be needed to invalidate the reported findings. Similarly, the respective funnel plots were not asymmetrical (Figures S1 and S2) and the Excess Significance Tests were not significant (ps>.95). The heterogeneity analyses revealed very low between-study heterogeneity for the dorsolateral prefrontal cortex (I^2=.00) and low to medium for the orbitofrontal cortex (I^2=.44).

Meta-regression analyses: Associations with PCL-R Total, Factors 1 and 2

Higher Total and Factor 1 and 2 scores were only associated with decreased GMV, notably decreased GMV in the left dorsolateral and orbitofrontal cortices. Specifically, higher Total psychopathy scores were associated with decreased GMV in the left dorsolateral prefrontal cortex, left medial orbitofrontal cortex, mid/posterior cingulate, left pre/postcentral gyri, right inferior temporal gyrus and left caudate (Figure S4, Table S3). Higher Factor 1 scores were related to decreased GMV in the left dorsolateral prefrontal cortex, bilateral medial orbitofrontal cortex, left supplementary motor area (extending into mid/posterior cingulate), left inferior frontal gyrus, bilateral inferior temporal gyrus, and left precentral gyrus (Figure S5, Table S3). Higher Factor 2 scores were related to decreased GMV bilaterally in the caudate and in the middle/inferior temporal gyri, left middle occipital gyrus, left dorsolateral prefrontal cortex, left medial orbitofrontal cortex, left mid/posterior cingulate, left pre/postcentral gyrus, as well as right rolandic operculum (Figure S6, Table S3). At the request of the handling Editor, we also conducted two additional meta-regressions, one for each Factor, while controlling for the other Factor. Given existing concerns in the field regarding this type of analyses (Lynam, Hoyle, & Newman, 2006) and the lack of consistency in the use of those analyses across the neuroimaging studies focusing on psychopathy, their results (Table S7) would be problematic to interpret and thus are not discussed in the manuscript.

Functional Characterization

Group comparison. The left dorsolateral prefrontal cortex was significantly associated with explicit memory and social cognition within the cognitive domain whereas the medial orbitofrontal cortex was significantly related to reward processing within the emotion domain, reasoning and language within the cognition domain, and gustation within the perception domain (Figure 2).

Meta-regressions. For Total psychopathy, aside from the left dorsolateral and orbitofrontal cortices identified above in the group comparison, the mid/posterior cingulate gyrus cluster was related to anxiety within the negative emotion domain, whereas the postcentral gyrus cluster was related to the action execution and the precentral gyrus clusters to action execution/imagination and perception domains (Figure S4). No significant domain associations were observed for the right inferior temporal gyrus and the left caudate. For Factor 1, the left supplementary motor area cluster (extending into mid/posterior cingulate) was related to anxiety within the emotion domain, whereas the left middle inferior frontal gyrus cluster was related to gustation within the perception domain (Figure S5). No significant domain associations emerged for the right medial orbitofrontal cortex, bilateral inferior temporal gyrus, and left precentral gyrus. For Factor 2, the right caudate cluster was related to reward/gain processing within the positive emotion domain and reasoning within the cognition domain, whereas the left middle occipital gyrus was related to vision shape, spatial processing, and observation within the perception, cognition, and action domains, respectively (Figure S6). The right rolandic operculum cluster was related to pain within the perception domain (Figure S6). No significant domain associations were detected for left caudate, bilateral middle/inferior temporal gyri, left mid/posterior cingulate, and left pre/postcentral gyrus.

Discussion

This is the first meta-analysis of VBM studies investigating GMV in psychopathy and as such constitutes to date the largest investigation examining the association between psychopathy and GMV. Compared to controls, individuals with psychopathy exhibited significantly reduced GMV within the left hemisphere in the dorsolateral prefrontal and orbitofrontal cortices. Across the seven studies we did not identify any publication bias. Finally, meta-regressions across 11 studies (N=519 individuals) revealed that Total

psychopathy scores as well as Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures. Below we discuss those regions in relation to the two neurobiological models of psychopathy (Blair, 2013; Kiehl, 2006) and the domains identified by our functional characterization that have been found to be central to psychopathy in previous experimental work.

Men with psychopathy exhibited reduced GMV in the left dorsolateral prefrontal cortex, which our functional characterization identified as being related to explicit memory and social cognition within the cognitive domain. This finding fits with behavioral evidence of impairments in psychopathy on tasks tapping explicit memory abilities such as working memory (De Brito, Viding, Kumari, Blackwood, & Hodgins, 2013) and emotional autobiographical memory (Lanciano, Curci, & Basile, 2019), as well as deficits on tasks indexing aspects of social cognition such as emotional face processing (Dawel et al., 2012), empathy (Blair, 2018), moral judgment (Marshall, Watts, & Lilienfeld, 2018), and spontaneous perspective taking (Drayton, Santos, & Baskin-Sommers, 2018). While no fMRI study prompting explicit memory exists in psychopathy, our meta-analytic data align with evidence of atypical brain response in the dorsolateral prefrontal cortex in individuals with psychopathy during social cognition tasks requiring the processing of facial expressions of emotions (Contreras-Rodríguez et al., 2013), imagining other's perspective (Decety, Chen, Harenski, & Kiehl, 2013) and making moral judgments (Pujol et al., 2012). GMV reduction in this region was related to higher PCL-R Total and both Factors' scores suggesting that abnormalities in those various aspects of social and cognitive domains might underpin both the profound affective-interpersonal and behavioral difficulties seen in psychopathy (Hare & Neumann, 2008).

Our meta-analysis also revealed that individuals with psychopathy were characterized by GMV reduction in the left orbitofrontal cortex, which our functional characterization identified as central to reward processing within the emotion domain, language and reasoning within the cognition domain, and gustation within the perception domain. GMV reduction within the orbitofrontal cortex is consistent with several emotion-based neurocognitive models of psychopathy, such as the Somatic Marker Hypothesis (Damasio, Tranel, & Damasio, 1990) or the more recent Integrated Emotion Systems (Blair et al., 2005), which significantly rest on neuropsychological and behavioral data (e.g., passive avoidance learning, response reversal and decision-making paradigms) documenting aberrant processing of reward information in patients with lesions to the orbitofrontal cortex and individuals with psychopathy (Blair et al., 2005). A small body of fMRI work also suggests that antisocial behavior in general, and psychopathy in particular, is also linked with aberrant response within the orbitofrontal cortex during reward processing (Murray, Waller, & Hyde, 2018). Our functional characterization also suggested that GMV reduction in this structure is related to language and reasoning within the cognitive domain. As such, these data align with early cognitive research examining the use of linguistic information in individuals with psychopathy and showing abnormal processing of semantic and affective information in this population (Hiatt & Newman, 2006). Indeed, one of the most replicated findings in this line of work is the lack of affective facilitation of individuals with psychopathy when processing affective words. This poor integration of cognitive and emotional information has been identified early as hallmark of psychopathy and referred to as 'semantic dementia' (Cleckley, 1976) to reflect the fact the psychopath 'knows the words but not the music'(p.217; (Johns & Quay, 1962).

Based on evidence that psychopathy lies on a continuum (Hare & Neumann, 2008) and that the two factors index different dimensions of the disorder (Hare, 2003), we

conducted meta-regression analyses based on the Total psychopathy, Factor 1 and 2 scores. The three sets of scores were all related to decreased GMV within the dorsolateral and orbitofrontal cortices, as well as with decreased GMV across the three other lobes and within the caudate. Specifically, Total, Factors 1 and 2 scores were all associated with decreased volume of the mid/posterior cingulate gyrus, a paralimbic region central to one of the two neurobiological models of psychopathy (Kiehl, 2006), that our functional characterization linked to anxiety within the negative emotion domain. This finding is interesting given the current debate about the place of anxiety within the construct of psychopathy as operationalized by the PCL-R (Hare, Neumann, & Mokros, 2018). Higher Total psychopathy score was also related to decrease volume of the postcentral and precentral gyri, regions central to action (execution/imagination) and perception domains according to our functional characterization. Thus, these GMV reduction could be related the impaired empathy (Blair, 2018) or response inhibition (Blair et al., 2005) seen in the disorder. Indeed, GMV decreases in those regions fit with fMRI work showing modulation of activation in the same regions in individuals with psychopathy when asked to watch versus empathize with an actor experiencing pain (Meffert, Gazzola, den Boer, Bartels, & Keysers, 2013) and as such could be related the profound lack of empathy that is central to the disorder. GMV reduction in those regions could also be related to the well-established impairment seen on response inhibition tasks (i.e., action withholding and action cancellation) seen in psychopathy (Blair et al., 2005) given the involvement of those regions in those tasks (Zhang, Geng, & Lee, 2017). Higher Factor 1 was also related to decrease GMV in the left supplementary motor area (extending into mid/posterior cingulate) and in the left middle inferior frontal gyrus, which, as noted earlier, could be related to data previously discussed on anxiety in the emotion domain.

Higher Factor 2 scores was related to lower volume of the caudate, which forms part of the dorsal striatum and our functional characterization linked to the reward and gain processing in gambling paradigms within the positive emotion domain and reasoning within the cognition domain. In the Integrated Emotion Systems of psychopathy (Blair, 2013), abnormalities within the caudate are thought to be central to the development of psychopathy and there is a wealth of data showing that both youth with psychopathic traits and adults with psychopathy are characterized by abnormalities in reward processing in gambling tasks (Blair et al., 2005). For example, impairments on the Iowa Gambling Task, which recruits the caudate during its anticipation phase (Lin, Chiu, Cheng, & Hsieh, 2008), has been documented in those populations (Blair et al., 2005), with some evidence that it is related to the antisocial-impulsive component of the disorder (Beszterczey, Nestor, Shirai, & Harding, 2013). Similarly, a small body of fMRI work has shown that Factor 2 is related to ventral and dorsal striatum response when anticipating reward (Murray et al., 2018) and processing rewarding stimuli (Cope et al., 2014), respectively. Higher Factor 2 was also associated with lower GMV within the left middle occipital gyrus, which our functional characterization linked to vision shape, spatial processing, and observation within the perception, cognition, and action domains, respectively. While abnormalities within occipital regions are not predicted by the two neurobiological models of the disorder, our results align well with those of a number of task-based fMRI studies reporting abnormal response in this region in individuals with psychopathy during the processing of affective pictures (Muller et al., 2003), static (Contreras-Rodríguez et al., 2014) and dynamic (Decety, Skelly, Yoder, & Kiehl, 2014) emotional faces. Interestingly, three fMRI studies have reported reduced functional connectivity between the occipital cortex and cortical (Juárez, Kiehl, & Calhoun, 2013) and subcortical structures (i.e., amygdala (Contreras-Rodríguez et al., 2013) and caudate (Korponay et al., 2017a)) in individuals with psychopathy, with two of those studies relating

reduced connectivity to Factor 2. These data thus suggest that this *network* maybe be important in the manifestations of the impulsive-antisocial aspects of the disorder, which might need to be considered in the future for refining the two neurobiological models of the disorder.

Taken together, the above associations with GMV in cortical and subcortical regions could partly account for the wide range of domains that are impaired in the disorder, as suggested by our functional characterization analysis. However, several aspects of our findings are worth noting. First, none of the clusters we identified, both in the main meta-analysis and in our meta-regressions, overlap with those identified by the two recent meta-analyses of fMRI data on psychopathy (Deming & Koenigs, 2020; Poeppl et al., 2018), suggesting a potential dissociation between structural and functional brain abnormalities in psychopathy.[1] Second, most of the regions associated with psychopathy were located within the left hemisphere, whose functioning has been identified as impaired in experimental work (Hiatt & Newman, 2006) prompting the left hemisphere cognitive model of psychopathy (Lopez, Kosson, Weissman, & Banich, 2007). Third, our meta-regressions for Factors 1 and 2 revealed that, while some regions of decreased GMV (e.g., dorsolateral and orbitofrontal cortices) were associated increased scores on both factors, reduction in GMV in some regions was unique to one factor (e.g., striatum and Factor 2), tentatively suggesting that the two factors of psychopathy might be associated with partially different pathophysiological processes (Yang and Raine, 2018). Fourth, from a neurodevelopmental perspective, the lack of association (both in the group and dimensional analyses) with GMV in the amygdala, a region central to the neurobiological models of psychopathy (Blair, 2013; Kiehl, 2006), is interesting and puzzling given previous neuroimaging meta-analyses in youths with conduct

[1] It is also possible that this discrepancy reflects the fact that those meta-analyses included a larger number of studies, which, in addition to forensic and clinical samples, also included non-clinical/non-forensic samples assessed via self-report measures of psychopathic traits.

problems reporting both structural and functional abnormalities within that region (Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015; Rogers & De Brito, 2016), with some of them reporting an association between callous-unemotional traits and amygdala volume (Rogers & De Brito, 2016) or response (Dugré et al., 2020). A similar pattern of more severe abnormalities in youths compared to adults for emotion processing, for which the amygdala plays a central role, has been reported in another meta-analysis (Dawel et al., 2012). There is also evidence from meta-analytic work in ADHD that adults might not present amygdala GMV reductions that have been observed in youths (Hoogman et al., 2017). It is not clear, however, if those discrepancies between youth and adult data reflect true developmental effects or the influence of confounding variables associated with age (e.g., sample characteristics); prospective longitudinal studies starting in childhood are needed to address those competing hypotheses, which could help to specify the two neurobiological models of psychopathy. Finally, from a theoretical standpoint, no effect of psychopathy on amygdala volume is also worth discussing given that two recent meta-analyses of fMRI studies have identified abnormal amygdala response in psychopathy (Deming & Koenigs, 2020; Poeppl et al., 2018), albeit in opposite directions. It should also be noted that of the seven studies included in our main meta-analysis, only one (Contreras-Rodríguez et al., 2015) reported amygdala volume difference (i.e., decrease) in individuals with psychopathy compared to controls and, similarly, out of the 11 studies included in our meta-regressions, only one (Ermer et al., 2012) found an association (negative) between total psychopathy score and amygdala volume. In this context, our findings suggest that psychopathy might be more reliably associated with functional abnormalities of the amygdala, rather than structural ones, at least as measured by VBM methods. Again, prospective longitudinal studies collecting both structural and functional MRI data on the same participants over time are needed to clarify this issue. For now, our data might be useful to refine existing neurobiological models

of psychopathy by more precisely specifying the nature of amygdala abnormalities characterizing the disorder (Blair, 2013; Kiehl, 2006).

Limitations

First, unpublished studies were not included (although we did include unpublished results computed using data from Korponay et al., 2017), but the Orwins fail-safe *N* (Orwin, 1983) analysis and our funnel plots suggest that a potential publication bias is unlikely. Second, the total sample of this meta-analysis of VBM studies is smaller than others on antisocial youths (Raschle et al., 2015; Rogers & De Brito, 2016), but this reflects the fact that few group sMRI studies, some with particularly low number of participants (and likely underpowered), have been conducted on this hard-to-recruit population and underscores the need for a meta-analysis. This problem has often been referred to as 'garbage in, garbage out' (Borenstein, Hedges, Higgins, & Rothstein, 2009), whereby poor quality of the raw material included in a meta-analysis can lead to poor quality of the findings. We tried to mitigate this as much as possible by including the SPMs of the majority of the studies and by running of number of diagnostic checks (e.g., publication bias and heterogeneity analyses[2]), but ultimately we were constrained by the available data. This means that even our diagnostic indices should be interpreted with caution, as some of them (e.g., I^2) can be biased in small meta-analyses (von Hippel, 2015). Notwithstanding this limitation, we believe that the results of our meta-analysis are more informative than those of the individual studies included in this meta-analysis because we provide a quantitative estimate of the effects across this small body of literature. Third, because VBM cannot detect spatially complex and subtle group differences in other brain metrics such as cortical thickness and surface area (Alegria, Radua,

[2] Unlike previous versions of SDM, SDM-PSI does not offer the option to run a Jack-knife reliability analysis because the revised algorithm is significantly more computationally demanding. However, running a Jack-knife analysis on our results using a previous version of SDM revealed that the decreased GMV in the two prefrontal regions were reliable, as they were preserved in all but two (for dorsolateral prefrontal cortex) and one (for orbitofrontal cortex) study combinations (see Supplementary methods S3 and Table S4).

& Rubia, 2016), our results are inherently tied to the limitation of this method. However, our results of decreased GMV in prefrontal, temporal and midline structures being related to higher psychopathy scores are broadly consistent with those of several surface-based morphometry studies that reported cortical thickness reduction in the prefrontal (Kolla, Patel, Meyer, & Chakravarty, 2017) and temporal cortices (Ly et al., 2012), as well as reduced folding in the midcingulate in individuals with psychopathy (Miskovich et al., 2018). Fourth, the included studies only focused on males, meaning that our results might not be applicable to females with psychopathy. Fifth, we do not report effect sizes, but unfortunately this is not something that is currently available for the Seed-based d Mapping with Permutation of Subject Images method we used here (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). However, we note that effect sizes are not commonly reported in neuroimaging meta-analyses that have adopted other approaches (e.g., Activation Likelihood Estimation [ALE] or Multilevel Kernel Density Analysis [MKDA]). In fact, neither of the two recent meta-analyses of fMRI studies on psychopathy reported effect sizes (Deming & Koenigs, 2020; Poeppl et al., 2018). Indeed, for non-neuroimaging meta-analyses, the size of the effects is central, but neuroimaging meta-analyses are conceptually different, as they mostly test for spatial convergence of effects across studies with the null-hypothesis of random spatial convergence (Müller et al., 2018). Finally, the seven studies differed in sample size, as well as potential comorbid psychopathologies, which might have influenced our results. Notably, the individuals with psychopathy in all the studies had a comorbid lifetime substance use disorder, meaning that we cannot rule out that some of the findings, like the effect in the orbitofrontal cortex recently reported in large mega-analysis of substance dependence (Mackay et al., 2019), could partially reflect substance use disorder. Unfortunately, we could not formally test this in our meta-analysis for two reasons. First, it was not possible to run a sub-group analysis because all of the studies included individuals with psychopathy with a

comorbid lifetime substance use disorder. Second, because the proportion of individuals with substance use disorders could not be obtained for each study, we could not run a moderation analyses similar to what was done for ADHD in our previous meta-analysis (Rogers & De Brito, 2016).

Conclusions

Bearing in mind the above limitations, the results from our meta-analysis suggest that, compared to controls, individuals with psychopathy exhibit reliable GMV reductions within dorsolateral prefrontal and orbitofrontal cortices in the left hemisphere. Total psychopathy scores as well as Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures, which likely account for the impairments in the emotion, cognition, action and perception domains seen in the disorder.

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Figure 1: PRISMA 2009 flow chart summarizing the study selection procedure

Figure 2. Clusters of decreased GMV for individuals with psychopathy (N=136) compared to controls (N=150) in the left dorsolateral and left medial orbitofrontal cortices. Slices are shown in the axial plane with MNI coordinates of the selected slices representing the peak in the z direction (see Table 2 for further details). Panels on either side describe the functional characterization for those two regions based on significant associations with psychological

terms (behavioral domains and paradigm classes) from BrainMap metadata. Reverse inference determined the above-chance probability of association with a behavioral function given observed brain activity in the respective region ($p < 0.05$, FDR corrected). The base rate denotes the general probability of finding BrainMap activation in the region. The x-axis indicates relative probability values.

Table 1: Characteristics of the 7 studies included in the main meta-analysis

No	Study	No. of Individuals with psychopathy	Age Individuals with psychopathy, Mean(SD)	IQ/*Education* [a] Individuals with psychopathy, Mean(SD)	No. Control Participants	Age Control Participants, Mean(SD)	IQ/*Education*[a] Control participants, Mean(SD)	Sample	Psychopathy Assessment	Lifetime Comorbidities	Scanner Strength	FWHM, mm	P Value
1	(de Oliveira-Souza et al., 2008)[b]	15	32.0(14.0)	*11.0(2.0)*	15	32.0(13.0)	*11.0(2.0)*	Community	PCL-SV	SUD	1.5	8	P<.005 uncorrected
2	(Müeller et al., 2008)[b]	17	33.00(5.81)	*10.8(2.4)*	17	30.59(5.92)	*15.4(2.8)*	Forensic patients	PCL-R	SUD	1.5	10	P<0.001 uncorrected
3	(Tiihonen et al., 2008)[b]	12	33.0(8.6)	94.7(8.6)	25	34.6(10.8)	NA	Pre-trial	PCL-R	SUD	1.0	8	P<0.05 corrected
4	(Bertsch et al., 2013)	12	27.3(5.4)	97.6(9.1)	14	26.1(8.3)	103.5(10.3)	Prison	PCL-R	BPD; SUD, PTSD, dyslexia, paedophelia	1.5	8	P<.005 uncorrected
5	(Gregory et al., 2012)	17	38.9(9.4)	89.9(11.7)	22	32.4(7.7)	99.4 (12.9)	Probation	PCL-R	SUD, PD cluster A, B, C	1.5	8	P<.05 cluster corrected
6	(Contreras-Rodríguez et al., 2015)	22	39.8(9.2)	*9.0(2.7)*	22	40.6(9.5)	*10.5(2.3)*	Prison	PCL-R	SUD	1.5	8	P<.05 cluster corrected
7	(Korponay et al., 2017b)	41	31.5(7.7)	101.5(10.3)	35	31.3(7.9)	97.3(12.0)	Prison	PCL-R	SUD	1.5	8	P<.05 cluster corrected

Notes. Abbreviations: BPD = Borderline Personality Disorder; PD = Personality Disorder; IQ = Intelligence Quotient; SUD: Substance use disorders; FWHM = full-width half-maximum; PCL-SV = Psychopathy Checklist: Screening Version; PCL-R= Psychopathy Checklist – Revised; PTSD = Post-Traumatic Stress Disorder

[a] Years of education as reported in each study (please note that the criteria for what counts as a year in education might not be consistent across studies)

[b] Studies for which raw SPMs were not available.

Table 2: Meta-analysis results comparing GMV in individuals with psychopathy (N=136) to controls (N=150)

Anatomical Location[a]	Hemisphere	MNI Coordinates (x, y, z)	SDM Z value	*P* Value[b]	Effect Size (SDM Estimate)[c]	No. of voxels
Individuals with psychopathy < Controls						
Superior Frontal Gyrus (Dorsolateral, BA 9/10/46)	**Left**	**-22,54,22**	**-2.530**	**.013**	**-0.423**	**353**
Superior/Middle/Rectus Frontal, Gyrus (Medial Orbital part BA 10/11)	**Left**	**-14,32,-16**	**-2.445**	**.022**	**-0.295**	**239**
Superior/Middle/Rectus Frontal Gyrus (Medial Orbital part BA 10/11)	Left	-14,28,-14	-2.264	.029		
Superior Frontal (Orbital BA 11)	Left	-6,36,-10	-2.208			

Note: MNI = Montreal Neurological Institute; SDM = signed differential mapping; ASPD+P = antisocial personality disorder with psychopathy; BA = Brodmann area.

[a] Areas shown in **BOLD** reflect the peak anatomical location with the breakdown of local peaks within this cluster also shown.

[b] Threshold-Free Cluster Enhancement correction

[c] The SDM estimate values, equivalent to the effect size, are reported for the cluster peaks.

Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis

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Abstract

Voxel-based morphometry (VBM) studies of gray matter volume (GMV) in psychopathy have produced inconsistent results and few have been replicated. Therefore, to clarify GMV abnormalities associated with psychopathy as operationalized by Hare (2003), we conducted a meta-analysis of VBM studies using both categorical and dimensional analyses. We identified 7 studies eligible for the categorical meta-analysis (136 men with psychopathy vs 150 male controls ~~men~~) and 11 studies (N=519) eligible for dimensional meta-regressions. First, we used Seed-based *d* Mapping with Permutation of Subject Images for voxel-based meta-analyses. Statistical parametric maps (SPMs) of GMV were available for 4 (57%) of the studies included in the categorical meta-analysis and for 5 (45%) of the studies included in the dimensional meta-regression analyses, with peak coordinates available for the remaining studies. Second, ~~employing~~ we used meta-data of a large-scale neuroimaging database to provide an objective and quantitative account of psychological processes attributed to the brain regions we identified in our group meta-analysis and meta-regressions., ~~we statistically assessed their physiological mental functions.~~ Men with psychopathy exhibited reliable GMV abnormalities circumscribed to the left hemisphere in the dorsolateral prefrontal cortex and the medial orbitofrontal cortex. Total psychopathy scores, Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures. We discuss how decreased GMV in those regions likely account for the impairments in the emotion, cognition, action and perception domains seen in the disorder.

Key words: Psychopathy; gray matter volume; voxel-based morphometry; meta-analysis; signed differential mapping.

General Scientific Summary: This review shows that psychopathy and specific dimensions of the disorder are associated with gray matter volume decreases in two prefrontal regions, as

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well as a wider set of regions including midline, temporal, parietal, occipital and subcortical structures.

Cortical and subcortical gray matter volume in psychopathy: A voxel-wise meta-analysis

Psychopathy is a personality disorder that manifests as a syndrome characterized by a constellation of affective (e.g., lack of empathy and remorse, and callousness), interpersonal (e.g., grandiosity, glibness, superficial charm, and the manipulation of others) and behavioral characteristics (e.g., impulsivity, early behavioral problems/delinquency and criminal versatility) (Hare & Neumann, 2008). In comparison to ~~non-psychopaths~~individuals without psychopathy, ~~psychopaths~~ those with psychopathy start offending younger (Wong, 1985), exhibit more instrumental aggression (Porter & Woodworth, 2006), are more often convicted or charged for violent offences (Hare & McPherson, 1984; Kosson, Lorenz, & Newman, 2006), and are more likely to reoffend following release (Hemphill, Hare, & Wong, 1998). Consistent with those behavioral features, ~~psychopaths~~individuals with psychopathy exhibit emotional (Kosson et al., 2006) and cognitive impairments (Mitchell et al., 2006), ~~and~~ as well as abnormal neural responses (Deming & Koenigs, 2020; Poeppl et al., 2018; Verona, Sprague, & Sadeh, 2012) that have been related to socio-affective dysfunction and poor decision-making (e.g., (Hosking et al., 2017).

These behavioral, experimental and functional neuroimaging data, together with neuropsychological studies examining the above domains (Blair, Mitchell, & Blair, 2005), suggest that the clinical presentation of psychopathy and its functional impairments might be underpinned by structural abnormalities in a network of cortical and subcortical regions (Blair & Zhang, 2020; Pera-Guardiola et al., 2016). Consistent with this view, Pera-Guardiola and colleagues recently showed in ~~psychopaths~~individuals with psychopathy that lower grey matter volume (GMV) in the prefrontal cortex (orbitofrontal, inferior frontal, and dorsomedial), somatosensory cortex, anterior insula, cingulate cortex, and cerebellum were

related to poorer recognition of facial expressions of emotions (Pera-Guardiola et al., 2016);, a reliable impairments in psychopathy (Dawel, O'Kearney, McKone, & Palermo, 2012).

A small number of structural MRI studies have used automated and unbiased methods, such as voxel-based morphometry (VBM), to characterize whole-brain and regional GMV in psychopathsindividuals with psychopathy. Intriguingly, no overall differences between psychopathsindividuals with psychopathy and controls have been reported for total intracranial volume (Contreras-Rodríguez et al., 2015; Pera-Guardiola et al., 2016; Tiihonen et al., 2008), or total GMV (Contreras-Rodríguez et al., 2015; Pera-Guardiola et al., 2016; Schiffer et al., 2011), but a number of studies did not report this information (Bertsch et al., 2013; de Oliveira-Souza et al., 2008; Gregory et al., 2012; Müeller et al., 2008). Those studies, however, have reported that psychopathsindividuals with psychopathy are characterised by reduced GMV across several cortical and subcortical regions (for reviews, see Johanson,Vaurio, Tiihonen, & Lähteenvuo, 2019; Pujol, Harrison, Contreras-Rodriguez, & Cardoner, 2019). Cortical regions , includeing frontal (medial/lateral orbital, superior, dorsal, medial, polar, and lateral subregions)(Bertsch et al., 2013; Contreras-Rodríguez et al., 2015; de Oliveira-Souza et al., 2008; Gregory et al., 2012; Müeller et al., 2008; Tiihonen et al., 2008), , temporal (superior, middle, inferior, and fusiform) (Bertsch et al., 2013; Contreras-Rodríguez et al., 2015; de Oliveira-Souza et al., 2008; Gregory et al., 2012; Müeller et al., 2008; Tiihonen et al., 2008), parietal (inferior lobule)(Müeller et al., 2008), occipital (Bertsch et al., 2013; de Oliveira-Souza et al., 2008), as well as anterior (Müeller et al., 2008)/ and posterior (Bertsch et al., 2013; de Oliveira-Souza et al., 2008; Müeller et al., 2008) cingulatee, and anterior (Contreras-Rodríguez et al., 2015; de Oliveira-Souza et al., 2008; Schiffer et al., 2011; Tiihonen et al., 2008) and posterior (de Oliveira-Souza et al., 2008; Gregory et al., 2012; Pera-Guardiola et al., 2016) insular cortices. Subcortical regions include the, amygdala (Contreras-Rodríguez et al., 2015), hippocampus (Contreras-Rodríguez

et al., 2015), and striatal regions, notably the caudate (de Oliveira-Souza et al., 2008; Tiihonen et al., 2008) and putamen (de Oliveira-Souza et al., 2008). We note, however, that one study has also reported increased GMV in the caudate (Schiffer et al., 2011) and the amygdala (Schiffer et al., 2011) of psychopathsbeingto be associated with higher psychopathy scores. In sum, T this VBM literature shows that there are marked inconsistencies across studies in the foci of reduced GMV, which encompass the four lobes of the brain and several subcortical structures. As suchIn this context, a meta-analysis of those VBM data would constitute a valuable theoretical advance in this field by providing a better understanding of the structural underpinnings ofbrain regions reliably associated with psychopathy, which could in turn inform, and possibly refine, two neurobiological models of the disorder (Blair, 2013; Kiehl, 2006). The Integrated Emotion Systems (IES; (Blair, 2013) identifies the amygdala, striatum, and ventromedial prefrontal cortex as the core regions implicated in psychopathy whereas the Paralimbic Hypothesis (PDM; (Kiehl, 2006) includes a more widespread set of closely related regions (i.e., amygdala, orbitofrontal cortex, cingulate cortex, parahippocampal area, and insula), which share similar cytoarchitectonic features in terms of neuronal type, structure and density.

Possible causes for these inconsistent findings and lack of replication are variations in data analytic approaches and sample characteristics within and across studies. For example, the relatively small sample size for most, but not all (Gregory et al., 2012), studies could have resulted in low statistical power and increased risk of both type I and II errors (Button et al., 2013). Furthermore, psychopathy as defined by the PCL-R is underpinned by two correlated factors, with Factor 1 indexing the interpersonal and affective features of the disorder, while Factor 2 includes items assessing impulsivity and a chronic antisocial lifestyle (Hare & Neumann, 2008). However, several studies adopting a group-level design (i.e., psychopathsindividuals with psychopathy vs non-psychopathsthose without psychopathy)

(Bertsch et al., 2013; Gregory et al., 2012; Tiihonen et al., 2008) have failed to examine the association between factors of psychopathy and GMV abnormalities, with those that have reporting divergent patterns of associations with cortical GMV (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Pera-Guardiola et al., 2016; Schiffer et al., 2011). Finally, it must be noted that two recent meta-analyses of fMRI data on psychopathy either did not (Poeppl et al., 2018) or could not (Deming & Koenigs, 2020) examine the association between the two factors of psychopathy and ~~their results~~brain response, which is an important limitation (Latzman, Patrick, & Lilienfeld, 2020).

Consistent with the evidence that psychopathy lies on a continuum (Edens, Marcus, Lilienfeld, & Poythress, 2006; Guay, Ruscio, Knight, & Hare, 2007), five VBM studies (the two studies by Korpornay and colleagues used the same sample) have used dimensional analyses (i.e., regression or correlations analyses) to examine the association between the degree/severity of overall psychopathy (and its Factors) scores as measured by the PCL-R and GMV (Cope et al., 2012; Ermer, Cope, Nyalakanti, Calhoun, & Kiehl, 2012; Korponay et al., 2017a; Korponay et al., 2017b; Leutgeb et al., 2015). Two of those studies found that *Total psychopathy* scores were negatively correlated with GMV in temporal and limbic/paralimbic regions (Cope et al., 2012; Ermer et al., 2012), but divergent correlations were reported for prefrontal and subcortical regions (e.g., caudate, thalamus). In three of those studies (Cope et al., 2012; Ermer et al., 2012; Korponay et al., 2017b), PCL-R *Factors 1 and 2* scores were shown, respectively, to correlate negatively and positively with GMV, notably in the prefrontal cortex, suggesting that the two factors of psychopathy might be associated with different pathophysiological processes. However, there were also notable inconsistent findings across the five studies, notably in the prefrontal cortex, thus ~~reinforcing~~ supporting the need for -dimensional analyses ~~of~~ examining the association between psychopathy factors scores and GMV across those studies.

In this context, a meta-analysis of the VBM data in relation to psychopathy would constitute a valuable theoretical advance in this field by providing a better understanding of the nature and topography of the structural brain abnormalities *reliably* associated with psychopathy. Those data, in conjunction with the results of the two recent fMRI meta-analyses (Deming & Koenigs, 2020; Poeppl et al., 2018), could in turn inform, and possibly refine, the two neurobiological models of the disorder (Blair, 2013; Kiehl, 2006). The Integrated Emotion Systems (Blair, 2013) identifies the amygdala, striatum, and ventromedial/orbito prefrontal cortex as the core regions implicated in psychopathy whereas the Paralimbic Hypothesis (Kiehl, 2006) includes a more widespread set of closely related regions (i.e., amygdala, orbitofrontal cortex, cingulate cortex, parahippocampal area, and insula), which share similar cytoarchitectonic features in terms of neuronal type, structure and density. While both models identify the amygdala and the orbitofrontal cortex as a key regions, so far the VBM evidence is mixed. Furthermore, because most of the studies include small samples, both type I and II errors could detrimentally influence~~d~~ those models.

Therefore, ~~G~~given the~~se~~ inconsistent results in this literature, we did not formulate specific hypotheses and conducted meta-analyses on all published whole-brain VBM studies in psychopathy using Seed-based d Mapping with Permutation of Subject Images (SDM-PSI (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). Only whole-brain VBM studies were included to ensure that results were not biased or restricted to a priori regions of interest (Radua et al., 2012). To increase the accuracy and sensitivity of our analyses, we included the original SPMs from four (57%) of the studies included in our categorical meta-analysis (Radua et al., 2012). Diagnostic tests (publications bias and heterogeneity analyses) were performed to assess the robustness of our findings. Furthermore, we also conducted dimensional meta-regressions to examine the association between Total psychopathy, Factor 1 and 2 scores, and GMV ~~using the original SPMs from five (45%) of the studies~~

~~included~~across 11 studies including 519 participants. Finally, consistent with a recent meta-analysis of fMRI studies on psychopathy (Poeppl et al., 2018), in order to provide an objective and quantitative account of psychological processes attributed to the brain regions we identified in our group meta-analysis and meta-regressions, we statistically assessed their psych~~hysi~~ological mental functions. This was achieved by linking psychological processes to the identified regions using meta-data of a large-scale neuroimaging database of healthy participants. This objective process of combining functional localisation and characterisation provides an observer-independent link between pathophysiology and psychopathology.

Method

Search and Study Selection

A literature search of The PubMed, ScienceDirect, Scopus and Web-of-Science databases for VBM studies published in English language between 2008 – the year of the first three VBM studies in psychopathy (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Tiihonen et al., 2008) – and February 2020 was carried out by SADB and DM independently. The study selection procedure is summarized in Figure 1. Titles, abstracts, citations and reference lists of the outputted studies were assessed to determine relevance and to identify additional studies for inclusion. Studies were included in main meta-analysis if they (1) focused on psychopathy as defined by the PCL-R (or its screening version, the PCL:SV (Hart, Cox, & Hare, 1995)), (2) compared ~~psychopaths~~individuals with psychopathy to controls, and (3) used VBM to examine GMV. ~~Individuals~~ Participants were considered as ~~psychopaths~~individuals with psychopathy if they had diagnosis of psychopathy established via the PCL-R using the established cutoff scores in North America (i.e., 30) and Europe (i.e., 25). For the PCL:SV the cutoff score was 18. Studies were excluded (see Supplemental Table 1) from the main meta-analysis if they failed (1) to use VBM, (2) to report a voxel-wise comparison between ~~psychopaths~~individuals with psychopathy and controls for GMV, (3) did

not report whole-brain results, (4) used different significance or extent thresholds when reporting results across the whole brain, (5) included duplicated data sets, and (6) did not provide peak coordinates or SPMs after contact with the authors.

Studies were included in the meta-regression analyses if they (1) had a measure of psychopathy such as the PCL-R or PCL:SV, and (2) examined GMV using VBM. Exclusion criteria for the meta-regression analyses were the same as for the main meta-analysis, except for criterion 2). We contacted the corresponding authors to request the original SPMs (at height and extent thresholds of $p<.001$ uncorrected and 0 voxel, respectively, as recommended by (Albajes-Eizagirre, Solanes, Fullana, et al., 2019) and to obtain additional details where necessary).

Comparison of regional gray matter volumes

Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI; v.6.21) software (http://www.sdmproject.com/software/) (Albajes-Eizagirre, Solanes, Vieta, et al., 2019) was used for voxel-based meta-analyses, comparing GMV differences in ~~psychopaths~~individuals with psychopathy and controls. SDM-PSI enables original SPMs and peak coordinates to be combined with established meta-analytical statistics (Methods S1 and Figure S1) (Albajes-Eizagirre, Solanes, Vieta, et al., 2019). SPMs used in this meta-analysis refer to group-level results for the comparison between ~~psychopaths~~individuals with psychopathy and controls. Both positive and negative effects are reconstructed within the same map, thus preventing a particular voxel from appearing in opposite directions. These negative effects are also included in the meta-analyses (Radua et al., 2012). The inclusion of the SPMs increases the statistical power of the meta-analysis and provides a more accurate representation of the results (Radua et al., 2012). SPMs for the group-wise comparison were obtained for four (57%) of the seven included studies (Table 1), while for three studies (de Oliveira-Souza et al., 2008; Müeller et al., 2008; Tiihonen et al., 2008) peak coordinates of

significant group differences between ~~psychopaths~~individuals with psychopathy and controls were used.

All the studies, but one (Müeller et al., 2008), controlled for total intracranial volume (Bertsch et al., 2013; Contreras-Rodríguez et al., 2015; de Oliveira-Souza et al., 2008; Tiihonen et al., 2008), total brain volume (grey matter + white matter) (Korponay et al., 2017b), or total GMV either via their statistical analyses (as covariate of no interest; (Contreras-Rodríguez et al., 2015)) or via their pre-processing pipeline (performed via a non-linear deformation on the normalized segmented grey matter images; (Gregory et al., 2012; Schiffer et al., 2011)), so our meta-analysis's results reflect *regional* group differences as commonly reported in VBM studies (Ridgway et al., 2008).

Results are reported corrected for multiple comparisons using threshold-free cluster enhancement (TFCE) family-wise-error (FWE) correction ($p<.05$) to optimize sensitivity while adequately controlling for Type 1 errors (Albajes-Eizagirre, Solanes, Fullana, et al., 2019). Meta-analysis Of Observational Studies in Epidemiology (MOOSE; Table S5) (Stroup et al., 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Table S6) (Liberati et al., 2009) guidelines were followed.

Diagnostics: Publication bias and heterogeneity

Several diagnostics were examined to aid interpretation of the results. First, to assess whether the available literature is biased toward excluding studies with non-significant results, an Orwin's fail safe-analysis *N* (Orwin, 1983) was performed. Second, funnel plots were produced, and associated Excess Significance Tests (Ioannidis & Trikalinos, 2007) were computed. Third, to assess the heterogeneity among the results of the included studies, the I^2 index was calculated with values of .25, .50, .75 indicating low, medium, and high heterogeneity, respectively (Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006).

Meta-Regressions

Linear meta-regression analyses were used to examine the influence of: (i) psychopathy Total score, and psychopathy (ii) Factor 1 and (iii) Factor 2 scores on GMV. Because the assessment tools used to measure psychopathy differed across studies (Tables 1 and 2), PCL-R and PCL:SV Total and Factor 1 and 2 scores were converted to Percent of Maximum Possible (POMP) scores (Fischer & Milfont, 2010), consistent with our approach in a previous meta-analysis (Rogers & De Brito, 2016) (Methods S2 and Table S2).

SPMs for the meta-regression analyses were obtained for five (45%) of the 11 studies included (Table S2). For the remaining six studies, original SPMs were not available, so peak coordinates taken from correlational analyses with psychopathy Total and Factor 1 and 2 scores were used. The meta-regressions used a stricter threshold to control for false-positives (p<0.017, Bonferroni-corrected [.05/3] for the 3 meta-regressions described above) (Radua et al., 2012). For the meta-regressions the permutations (N=50 imputations) were conducted at the study-level exploring differences in the value of the moderators of interest (psychopathy Total, Factor 1 and 2 scores) at this level using the Freedman-Lane method for optimal statistical performance (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) and predicting values within the observed range of the computed variable (i.e. from -1 to 1)(Albajes-Eizagirre, Solanes, Vieta, et al., 2019; Radua et al., 2012). The output from the meta-regression linear models represents the amount of grey matter change per unit increase in moderators of interest (Total, Factor 1 and 2 scores).

Functional Characterization

The regions identified by our meta-analysis were then functionally characterized based on metadata from the BrainMap database (Laird et al., 2009, Laird et al., 2011, & Fox et al., 2002) using reverse inference, which tests the probability of a mental process being present, given knowledge that a particular brain region is activated. This approach involves

the identification of all experiments that activate the particular region of interest in healthy participants, and the analyses of the experimental meta-data describing the experimental settings that were employed in those experiments. This allows statistical inference on the type of tasks that evoke activation in the particular region of interest. BrainMap codes tasks along two dimensions. Behavioral domains (BD) describe the cognitive processes probed by an experiment and comprises the main categories action, cognition, emotion, interoception, and perception (http://www.brainmap.org/taxonomy/behaviors.html). Paradigm classes (PC) describe the specific task used. In the reverse inference approach, the functional profile was determined by identifying the most probable taxonomic label, given activation in a particular region of interest. This probability, [P(Task|Activation], can be derived from [P(Activation|Task], as well as P(Task) and P(Activation) using Bayes' rule. A chi-squared test was used to test significance [p<0.05, corrected for multiple comparisons using FDR].

Results

Included Studies and Sample Characteristics

Twenty-four potential studies were identified for inclusion in the meta-analysis. Seventeen studies were excluded from the main meta-analysis based on inclusion/exclusion criteria (Figure 1 and Supplement Table 1). Seven eligible studies (Table 1) included a direct comparison of GMV between ~~psychopaths~~individuals with psychopathy (N=136 M age=33.64 years; SD=8.59; range=18–64 years) and controls (N=150 M age=32.51 years; SD=9.02; range=18–61 years) and were thus included in the group meta-analysis. All the participants across the seven studies were males with three of those studies including prisoners. For the meta-regressions, 11 studies (Table S2) were included, seven of which were part of group meta-analysis described above. Those 11 studies included 519 participants (M age= 34.5 years; SD=8.9; range=18–64 years), out of which 30 were females from one study (Cope et al., 2012). Five of the 11 studies included prisoners. Finally, nine of the 11

studies used the PCL-R to assess psychopathy (*Total score*: M=24.8; SD=5.6; range=2.1–40; *Factor 1*: M=8.9; SD=3.0; range=0–16; *Factor 2*: M=13.4; SD=3.4; range=2.2–18), while the remaining two used the PCL:SV (*Total score*: M=14.5; SD=3.6; range=5-24; *Factor 1*: M=7.1; SD=2.6; range=2-12; *Factor 2*: M=7.4; SD=1.7; range=1–12).

Figure 1 about here

Table 1 about here

~~Psychopaths~~Individuals with psychopathy vs. controls: Gray matter differences

~~Psychopaths~~Individuals with psychopathy had decreased GMV in the left dorsolateral prefrontal and the left medial orbitofrontal cortices when compared to controls (Table 2; Figure 2).

Figure 2 about here

Table 2 about here

Publications Bias and Heterogeneity

Using Rosenthal (1979)'s threshold of unpublished studies exceeding $5n + 10$, where n represents the number of studies included in the meta-analysis, the Orwin's fail safe-analysis N (Orwin, 1983) for the direct comparison of GMV between ~~psychopaths~~individuals with psychopathy and controls indicated that a potential publication bias was unlikely, as 169 studies showing no effect would be needed to invalidate the reported findings. Similarly, the respective funnel plots were not asymmetrical (Figures S1 and S2) and the Excess Significance Tests were not significant ($ps>.95$). The heterogeneity analyses revealed very low between-study heterogeneity for the dorsolateral prefrontal cortex ($I^2=.00$) and low to medium for the orbitofrontal cortex ($I^2=.44$).

Meta-regression analyses: Associations with PCL-R Total, Factors 1 and 2

Higher Total and Factor 1 and 2 scores were only associated with decreased GMV, notably decreased GMV in the left dorsolateral and orbitofrontal cortices. Specifically, higher

Total psychopathy scores were associated with decreased GMV in the left dorsolateral prefrontal cortex, left medial orbitofrontal cortex, mid/posterior cingulate, left pre/postcentral gyri, right inferior temporal gyrus and left caudate (Figure S4, Table S3). Higher Factor 1 scores were related to decreased GMV in the left dorsolateral prefrontal cortex, bilateral medial orbitofrontal cortex, left supplementary motor area (extending into mid/posterior cingulate), left inferior frontal gyrus, bilateral inferior temporal gyrus, and left precentral gyrus (Figure S5, Table S3). Higher Factor 2 scores were related to decreased GMV bilaterally in the caudate and in the middle/inferior temporal gyri, left middle occipital gyrus, left dorsolateral prefrontal cortex, left medial orbitofrontal cortex, left mid/posterior cingulate, left pre/postcentral gyrus, as well as right rolandic operculum (Figure S6, Table S3). At the request of the handling Editor, we also conducted two additional meta-regressions, one for each Factor, while controlling for the other Factor. Given existing concerns in the field regarding this type of analyses (Lynam, Hoyle, & Newman, 2006) and the lack of consistency in the use of those analyses across the neuroimaging studies focusing on psychopathy, their results (Table S7~~xe~~) would be problematic to interpret and thus are not discussed in the manuscript.

Functional Characterization

Group comparison. The left dorsolateral prefrontal cortex was significantly associated with explicit memory and social cognition within the cognitive domain whereas the medial orbitofrontal cortex was significantly related to reward processing within the emotion domain, reasoning and language within the cognition domain, and gustation within the perception domain (Figure 2).

Meta-regressions. For Total psychopathy, aside from the left dorsolateral and orbitofrontal cortices identified above in the group comparison, the mid/posterior cingulate gyrus cluster was related to anxiety within the negative emotion domain, whereas the

postcentral gyrus cluster was related to the action execution and the precentral gyrus clusters to action execution/imagination and perception domains (Figure S4). No significant domain associations were observed for the right inferior temporal gyrus and the left caudate. For Factor 1, the left supplementary motor area cluster (extending into mid/posterior cingulate) was related to anxiety within the emotion domain, whereas the left middle inferior frontal gyrus cluster was related to gustation within the perception domain (Figure S5). No significant domain associations emerged for the right medial orbitofrontal cortex, bilateral inferior temporal gyrus, and left precentral gyrus. For Factor 2, the right caudate cluster was related to reward/gain processing within the positive emotion domain and reasoning within the cognition domain, whereas the left middle occipital gyrus was related to vision shape, spatial processing, and observation within the perception, cognition, and action domains, respectively (Figure S6). The right rolandic operculum cluster was related to pain within the perception domain (Figure S6). No significant domain associations were detected for left caudate, bilateral middle/inferior temporal gyri, left mid/posterior cingulate, and left pre/postcentral gyrus.

Discussion

This is the first meta-analysis of VBM studies investigating GMV in psychopathy and as such constitutes to date the largest investigation examining the association between psychopathy and GMV. Compared to controls, ~~psychopaths~~individuals with psychopathy exhibited significantly reduced GMV within the left hemisphere in the dorsolateral prefrontal and orbitofrontal cortices. Across the seven studies we did not identify any publication bias. Finally, meta-regressions across 11 studies (N=519 individuals) revealed that Total psychopathy scores as well as Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures. Below we

discuss those regions in relation to the two neurobiological models of psychopathy (Blair, 2013; Kiehl, 2006) and the domains identified by our functional characterization that have been found to be central to psychopathy in previous experimental work.

Men with psychopathy exhibited reduced GMV in the left dorsolateral prefrontal cortex, which our functional characterization identified as being related to explicit memory and social cognition within the cognitive domain. This finding fits with behavioral evidence of impairments in psychopathy on tasks tapping explicit memory abilities such as working memory (De Brito, Viding, Kumari, Blackwood, & Hodgins, 2013) and emotional autobiographical memory (Lanciano, Curci, & Basile, 2019), as well as deficits on tasks indexing aspects of social cognition such as emotional face processing (Dawel et al., 2012), empathy (Blair, 2018), moral judgment (Marshall, Watts, & Lilienfeld, 2018), and spontaneous perspective taking (Drayton, Santos, & Baskin-Sommers, 2018). While no fMRI study prompting explicit memory exists in psychopathy, our meta-analytic data align with evidence of atypical brain response in the dorsolateral prefrontal cortex in ~~psychopaths~~individuals with psychopathy during social cognition tasks requiring the processing of facial expressions of emotions (Contreras-Rodríguez et al., 2013), imagining other's perspective (Decety, Chen, Harenski, & Kiehl, 2013) and making moral judgments (Pujol et al., 2012). GMV reduction in this region was related to higher PCL-R Total and both Factors' scores suggesting that abnormalities in those various aspects of social and cognitive domains might underpin both the profound affective-interpersonal and behavioral difficulties seen in psychopathy (Hare & Neumann, 2008).

Our meta-analysis also revealed that ~~psychopaths~~individuals with psychopathy were characterized by GMV reduction in the left orbitofrontal cortex, which our functional characterization identified as central to reward processing within the emotion domain, language and reasoning within the cognition domain, and gustation within the perception

domain. GMV reduction within the orbitofrontal cortex is consistent with several emotion-based neurocognitive models of psychopathy, such as the Somatic Marker Hypothesis (Damasio, Tranel, & Damasio, 1990) or the more recent Integrated Emotion Systems (Blair et al., 2005), which significantly rest on neuropsychological and behavioral data (e.g., passive avoidance learning, response reversal and decision-making paradigms) documenting aberrant processing of reward information in patients with lesions to the orbitofrontal cortex and individuals with psychopathy (Blair et al., 2005). A small body of fMRI work also suggests that antisocial behavior in general, and psychopathy in particular, is also linked with aberrant response within the orbitofrontal cortex during reward processing (Murray, Waller, & Hyde, 2018). Our functional characterization also suggested that GMV reduction in this structure is related to language and reasoning within the cognitive domain. As such, these data align with early cognitive research examining the use of linguistic information in ~~psychopaths~~individuals with psychopathy and showing abnormal processing of semantic and affective information in this population (Hiatt & Newman, 2006). Indeed, one of the most replicated findings in this line of work is the lack of affective facilitation of ~~psychopaths~~individuals with psychopathy when processing affective words. This poor integration of cognitive and emotional information has been identified early as hallmark of psychopathy and referred to as 'semantic dementia' (Cleckley, 1976) to reflect the fact the psychopath 'knows the words but not the music'(p.217; (Johns & Quay, 1962). ~~Finally, the reduction in grey matter within the orbitofrontal cortex might also be linked with a small body of evidence indicating altered olfactory (Lapierre, Braun, & Hodgins, 1995) and taste (Mahmut & Banzer, 2020) perception in individuals with high psychopathic traits.~~

Based on evidence that psychopathy lies on a continuum (Hare & Neumann, 2008) and that the two factors index different dimensions of the disorder (Hare, 2003), we conducted meta-regression analyses based on the Total psychopathy, Factor 1 and 2 scores.

The three sets of scores were all related to decreased GMV within the dorsolateral and orbitofrontal cortices, as well as with decreased GMV across the three other lobes and within the caudate. Specifically, Total, Factors 1 and 2 scores were all associated with decreased volume of the mid/posterior cingulate gyrus, a paralimbic region central to ~~a~~ one of the two ~~prominent~~ neurobiological model~~s~~s of psychopathy (Kiehl, 2006), that our functional characterization linked to anxiety within the negative emotion domain. This finding is interesting given the current debate about the place of anxiety within the construct of psychopathy as operationalized by the PCL-R (Hare, Neumann, & Mokros, 2018). ~~Although, a lack of anxiety was originally thought to be a core characteristic of psychopath , a large body of clinical and experimental research indicates that psychopaths can be further subdivided into primary and secondary variants that are characterized by low and high anxiety levels, respectively . Two recent fMRI studies in adolescents and adults suggest that these variants might be associated with distinct neurocognitive mechanisms, but to date no sMRI studies have compared those variants.~~ Higher Total psychopathy score was also related to decrease volume of the postcentral and precentral gyri, regions central to action (execution/imagination) and perception domains according to our functional characterization. Thus, these GMV reduction could be related the impaired empathy (Blair, 2018) or response inhibition (Blair et al., 2005) seen in the disorder. Indeed, GMV decreases in those regions fit with fMRI work showing modulation of activation in the same regions in ~~psychopaths~~individuals with psychopathy when asked to watch versus empathize with an actor experiencing pain (Meffert, Gazzola, den Boer, Bartels, & Keysers, 2013) and as such could be related the profound lack of empathy that is central to the disorder. GMV reduction in those regions could also be related to the well-established impairment seen on response inhibition tasks (i.e., action withholding and action cancellation) seen in psychopathy (Blair et al., 2005) given the involvement of those regions in those tasks (Zhang, Geng, & Lee,

2017). Higher Factor 1 was also related to decrease GMV in the left supplementary motor area (extending into mid/posterior cingulate) and in the left middle inferior frontal gyrus, which, as noted earlier, could be related to data previously discussed on anxiety in the emotion domain. ~~and on data of impaired gustation in the perception domain, respectively.~~

Higher Factor 2 scores was related to lower volume of the caudate, which forms part of the dorsal striatum and our functional characterization linked to the reward and gain processing in gambling paradigms within the positive emotion domain and reasoning within the cognition domain. ~~Structural and functional~~ In the Integrated Emotion Systems of psychopathy (Blair, 2013), abnormalities within the caudate are thought to be central to the development of psychopathy ~~(Blair, 2013)~~ and there is a wealth of data showing that both youth with psychopathic traits and adults with psychopathy are characterized by abnormalities in reward processing in gambling tasks (Blair et al., 2005). For example, impairments on the Iowa Gambling Task, which recruits the caudate during its anticipation phase (Lin, Chiu, Cheng, & Hsieh, 2008), has been documented in those populations (Blair et al., 2005), with some evidence that it is related to the antisocial-impulsive component of the disorder (Beszterczey, Nestor, Shirai, & Harding, 2013). Similarly, a small body of fMRI work has shown that Factor 2 is related to ventral and dorsal striatum response when anticipating reward (Murray et al., 2018) and processing rewarding stimuli (Cope et al., 2014), respectively. ~~The association between higher Factor 2 and lower caudate volume in relation to reasoning abilities within the cognition domain is, however, a bit less straightforward, but, together with lower GMV within the prefrontal cortex, could partly be related to evidence of impaired executive functioning in psychopathy (Ogilvie, Stewart, Chan, & Shum, 2011) given the known role of the frontal-striatal network in this domain (Melrose, Poulin, & Stern, 2007).~~ Higher Factor 2 was also associated with lower GMV within the left middle occipital gyrus, which our functional characterization linked to vision

shape, spatial processing, and observation within the perception, cognition, and action domains, respectively. While abnormalities within occipital regions are not predicted by the two neurobiological ~~current~~ models of the disorder, our results align well with those of a number of task-based fMRI studies reporting abnormal response in this region in ~~psychopaths~~individuals with psychopathy during the processing of affective pictures (Muller et al., 2003), static (Contreras-Rodríguez et al., 2014) and dynamic (Decety, Skelly, Yoder, & Kiehl, 2014) emotional faces. Interestingly, three fMRI studies have reported reduced functional connectivity between the occipital cortex and cortical (Juárez, Kiehl, & Calhoun, 2013) and subcortical structures (i.e., amygdala (Contreras-Rodríguez et al., 2013) and caudate (Korponay et al., 2017a)) in ~~psychopaths~~individuals with psychopathy, with two of those studies relating reduced connectivity to Factor 2. These data thus suggest that this *network* maybe be important in the manifestations of the impulsive-antisocial aspects of the disorder, which might need to be considered in the future for refining the two neurobiological models of the disorder. ~~Finally, higher Factor 2 score was related to decreased volume of the right rolandic operculum, which forms part of the secondary somatosensory cortex implicated in pain perception. This result dovetails with previous fMRI work documenting reduced response in the secondary somatosensory cortex of psychopaths when experiencing pain (Birbaumer et al., 2005) and when watching videos of others in pain (Meffert et al., 2013).~~

Taken together, the above associations with GMV in cortical and subcortical regions could partly account for the wide range of domains that are impaired in the disorder, as suggested by our functional characterization analysis. However, several aspects of our findings are worth noting. First, none of the ~~regions~~ clusters we identified, both in the main meta-analysis and in our meta-regressions, overlap with those identified by the two recent meta-~~analysis~~ analyses of fMRI data on psychopathy (Deming & Koenigs, 2020; Poeppl et al., 2018)~~(Deming & Koenigs, 2020)~~, suggesting a potential dissociation between structural

and functional brain abnormalities in psychopathy.[1] Second, most of the regions associated with psychopathy were located within the left hemisphere, whose functioning has been identified as impaired in experimental work (Hiatt & Newman, 2006) prompting the left hemisphere cognitive model of psychopathy (Lopez, Kosson, Weissman, & Banich, 2007). ~~Finally~~Third, our meta-regressions for Factors 1 and 2 revealed that, while some regions of decreased GMV (e.g., dorsolateral and orbitofrontal cortices) were associated increased scores on both factors ~~(e.g., dorsolateral and orbitofrontal cortices)~~, reduction in GMV in some regions was unique to one factor (e.g., striatum and Factor 2 ~~and striatum~~), tentatively suggesting that the two factors of psychopathy might be associated with partially different pathophysiological processes (Yang and Raine, 2018). Fourth, from a neurodevelopmental perspective, the lack of association (both in the group and dimensional analyses) with GMV in the amygdala, a region central to ~~neurocognitive~~ the neurobiological models of ~~the~~ psychopathy (Blair, 2013; Kiehl, 2006), is interesting and puzzling given previous neuroimaging meta-analyses in youths with conduct problems reporting both structural and functional abnormalities within that region (Raschle, Menks, Fehlbaum, Tshomba, & Stadler, 2015; Rogers & De Brito, 2016), with some of them reporting an association between callous-unemotional traits and amygdala volume (Rogers & De Brito, 2016) or response (Dugré et al., 2020). ~~Similar~~A similar pattern of more severe abnormalities in youths compared to adults for emotion processing, for which the amygdala plays a central role, have been reported in ~~relation to psychopathic traits in youths~~another meta-analysis (Dawel et al., 2012). There is also evidence from meta-analytic work in ~~other externalizing disorders~~ADHD that adults might not present amygdala GMV reductions that have been observed in youths (Hoogman et al., 2017). It is not clear, however, if those discrepancies

[1] It is also possible that this discrepancy reflects the fact that ~~the meta-analysis by Poeppl and colleagues~~those meta-analyses included a larger number of studies, which, in addition to forensic and clinical samples, also ~~focused~~ included~~on~~ non-clinical/non-forensic samples assessed via self-report measures of psychopathic traits.

between youth and adult data reflect true developmental effects or the influence of confounding variables associated with age (e.g., sample characteristics); prospective longitudinal studies starting in childhood are needed to address those competing hypotheses, which could help to specify the two neurobiological models of psychopathy. Finally, from a theoretical standpoint, no effect of psychopathy on amygdala volume is also worth discussing given that ~~(but see and the~~ two recent meta-~~analysis~~ analyses of fMRI studies ~~identifying~~ have identified ~~reduced~~ abnormal amygdala response in psychopathy (Deming & Koenigs, 2020; Poeppl et al., 2018), albeit in opposite directions. ~~.~~ It should also be noted that of the seven studies included in our main meta-analysis, only one (Contreras-Rodríguez et al., 2015) reported amygdala volume difference (i.e., decrease) in individuals with psychopathy compared to controls and, similarly, out of the 11 studies included in our meta-regressions, only one (Ermer et al., 2012) found an association (negative) between total psychopathy score and amygdala volume. In this context, our findings ~~cannot be interpreted to suggest that this region is structurally intact in adult psychopathy~~suggest that psychopathy might be more reliably associated with functional abnormalities of the amygdala, rather than structural ones, at least as measured by VBM methods~~ and might instead reflect methodological limitations of the VBM methods~~. Again, prospective longitudinal studies collecting both structural and functional MRI data on the same participants over time are needed ~~here~~ to clarify this issue. For now, our data might be useful to refine existing neurobiological models of psychopathy by more precisely specifying the nature of amygdala abnormalities characterizing the disorder (Blair, 2013; Kiehl, 2006).

Limitations

First, unpublished studies were not included (although we did include unpublished results computed using data from Korponay et al., 2017), but the Orwins fail-safe *N* (Orwin, 1983) analysis and our funnel plots suggest that a potential publication bias is unlikely.

Second, the total sample of this meta-analysis of VBM studies is smaller than others on antisocial youths (Raschle et al., 2015; Rogers & De Brito, 2016), but this reflects the fact that few group sMRI studies, some with particularly low number of participants (and likely underpowered), have been conducted on this hard-to-recruit population and underscores the need for a meta-analysis. This problem has often been referred to as 'garbage in, garbage out' (Borenstein, Hedges, Higgins, & Rothstein, 2009), whereby poor quality of the raw material included in a meta-analysis can lead to poor quality of the findings. We tried to mitigate this as much as possible by including the SPMs of the majority of the studies and by running of number of diagnostic checks (e.g., publication bias and heterogeneity analyses[2]), but ultimately we were constrained by the available data. This means that even our diagnostic indices should be interpreted with caution~~s~~, as some of them (e.g., I^2) can be biased in small meta-analyses (von Hippel, 2015). Notwithstanding this limitation, we believe that the results of our meta-analysis are more informative than those of the individual studies included in this meta-analysis because we provide a quantitative estimate of the effects across this small body of literature. Third, because VBM cannot detect spatially complex and subtle group differences in other brain metrics such as cortical thickness and surface area (Alegria, Radua, & Rubia, 2016), our results are inherently tied to the limitation of this method. However, our results of decreased GMV in prefrontal, temporal and midline structures being related to higher psychopathy scores are broadly consistent with those of several surface-based morphometry studies that reported cortical thickness reduction in the prefrontal (Kolla, Patel, Meyer, & Chakravarty, 2017) and temporal cortices (Ly et al., 2012), as well as reduced folding in the midcingulate in ~~psychopaths~~individuals with psychopathy (Miskovich et al.,

[2] Unlike previous versions of SDM, SDM-PSI does not offer the option to run a Jack-knife reliability analysis because the revised algorithm is significantly more computationally demanding. However, running a Jack-knife analysis on our results using a previous version of SDM revealed that the decreased GMV in the two prefrontal regions were reliable, as they were preserved in all but two (for dorsolateral prefrontal cortex) and one (for orbitofrontal cortex) study combinations (see Supplementary methods S3 and Table S4).

2018). Fourth, the included studies only focused on males, meaning that our results might not be applicable to females with psychopathy. Fifth, we do not report effect sizes, but unfortunately this is not something that is currently available for the Seed-based d Mapping with Permutation of Subject Images method we used here (Albajes-Eizagirre, Solanes, Vieta, & Radua, 2019). However, we note that effect sizes are not commonly reported in neuroimaging meta-analyses that have adopted other approaches (e.g., Activation Likelihood Estimation [ALE] or Multilevel Kernel Density Analysis [MKDA]). In fact, neither of the two recent meta-analyses of fMRI studies on psychopathy reported effect sizes (Deming & Koenigs, 2020; Poeppl et al., 2018). Indeed, for non-neuroimaging meta-analyses, the size of the effects is central, but neuroimaging meta-analyses are conceptually different, as they mostly test for spatial convergence of effects across studies with the null-hypothesis of random spatial convergence (Müller et al., 2018). Finally, the seven studies differed in sample size, as well as potential comorbid psychopathologies, which might have influenced our results. Notably, the ~~psychopaths~~individuals with psychopathy in all the studies had a comorbid lifetime substance use disorder, meaning that we cannot rule out that some of the findings, like the effect in the orbitofrontal cortex recently reported in large mega-analysis of substance dependence (Mackay et al., 2019), could partially reflect substance use disorder. Unfortunately, we could not formally test this in our meta-analysis for two reasons. First, it was not possible to run a sub-group analysis because all of the studies included ~~psychopaths~~individuals with psychopathy with a comorbid lifetime substance use disorder. Second, because the proportion of individuals with substance use disorders could not be obtained for each study, we could not run a moderation analyses similar to what was done for ADHD in our previous meta-analysis (Rogers & De Brito, 2016).

Conclusions

Bearing in mind the above limitations, the results from our meta-analysis suggest that, compared to controls, ~~psychopaths~~individuals with psychopathy exhibit reliable GMV reductions within dorsolateral prefrontal and orbitofrontal cortices in the left hemisphere. Total psychopathy scores as well as Factors 1 and 2 scores were all related to decreased GMV within those two prefrontal regions, as well as decreased GMV in a wider set of regions encompassing midline, temporal, parietal, occipital and subcortical structures, which likely account for the impairments in the emotion, cognition, action and perception domains seen in the disorder.

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Figure 1: PRISMA 2009 flow chart summarizing the study selection procedure

Figure 2. Clusters of decreased GMV for ~~psychopaths~~individuals with psychopathy (N=136) compared to controls (N=150) in the left dorsolateral and left medial orbitofrontal cortices. Slices are shown in the axial plane with MNI coordinates of the selected slices representing the peak in the z direction (see Table 2 for further details). Panels on either side describe the functional characterization for those two regions based on significant associations with psychological terms (behavioral domains and paradigm classes) from BrainMap metadata. Reverse inference determined the above-chance probability of association with a behavioral function given observed brain activity in the respective region ($p < 0.05$, FDR corrected). The base rate denotes the general probability of finding BrainMap activation in the region. The x-axis indicates relative probability values.