nature mental health

Analysis

https://doi.org/10.1038/s44220-023-00032-0

A systematic review and meta-analysis of brain volume abnormalities in disruptive behaviour disorders, antisocial personality disorder and psychopathy

Received: 1 August 2022

Accepted: 1 February 2023

Published online: 22 March 2023

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Individuals with disruptive behaviour disorders in youth and antisocial personality disorder and psychopathy as adults share some clinical characteristics, but also diverge in important ways. Existing meta-analyses of structural imaging studies suggest abnormalities within these disorders; however, so far none has examined the role of variability. Here we performed a systematic review and meta-analysis to examine both variability (coefficient of variation ratio) and magnitude of brain volume differences between antisocial groups and healthy controls (quantified using Hedges' *g*). A comprehensive search was conducted of PubMed, EMBASE, Web of Science, Scopus and PsycINFO from inception to 31 January 2022 (pre-registered with PROSPERO, ID number CRD42021250980, registered 25 June 2021). We included studies which included individuals with disruptive behaviour disorder (± callous–unemotional traits) or antisocial personality disorder (± psychopathy), defined using standardized classificatory tools (Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria for disruptive behaviour disorders and antisocial personality disorder, Psychopathy Checklist: Revised or Psychopathy Checklist: Screening Version for psychopathy) and a healthy control group, and which had sufficient data to extract mean and standard deviations, or *t* or *P* values, for both groups. We measured the relative variability of brain regions in antisocial individuals compared with controls, by using the log coefficient of variability ratio. Between-group differences in mean volumes were quantified using standardized mean difference. Risk of bias was assessed using modified version of the Newcastle–Ottawa Scale for case–control studies. Twenty-three studies met inclusion criteria. In antisocial individuals, there was significantly increased variability for total grey matter ($Z = -2.6581$, $P = 0.0079$) and overall decreases in mean volume for total whole brain ($g = -0.41$; 95% confidence interval (CI) −0.67 to −0.15, $P = 0.0016$), total grey matter ($g = -0.6$; 95% CI −0.93 to −0.26, $P = 0.004$) and amygdala ($g = -0.89$; 95% CI −1.55 to −0.22, $P = 0.009$), compared with

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healthy controls. This suggests a key role for structural variability in clinical divergence within these disorders. The key limitations were lack of studies for some brain regions of interest, including insula, and inconsistent clinical phenotyping. Further studies should seek to specify how this neurobiological variability maps to clinical variability and whether this holds potential value as a biomarker to guide prognosis or treatment selection.

A small group of men commit most violent crimes[1,2]. They engage in a life-course-persistent pattern of antisocial behaviour[3] and meet diagnostic criteria for disruptive behaviour disorder (DBD, which includes conduct disorder and oppositional defiant disorder) in childhood and antisocial personality disorder (ASPD) in adulthood. Within this group of men, however, there is also considerable clinical variability. About one-third demonstrate higher levels of callous–unemotional (CU) traits[4,5], which have substantial heritability[6], from childhood. They begin offending at earlier ages and engage in a broader range and greater severity of offending[7]. In adulthood, they meet criteria for an additional diagnosis of psychopathy (ASPD + P)[8]. Notably, they also respond less well to psychosocial treatment programmes in childhood[9] and adulthood[10] than those without psychopathy (ASPD − P).

Emerging evidence suggests that the clinical features of DBD and ASPD may be underpinned by neurobiological abnormalities, from early in life. For instance, two meta-analyses of voxel-based morphometry (VBM) structural magnetic resonance imaging (MRI) studies of youths with DBD[11,12] have shown consistent reductions in grey matter volume across several cortical and subcortical regions. These include ventrolateral, medial prefrontal, middle temporal, superior temporal and anterior insular cortices, and amygdala, caudate and putamen. In adults, previous reviews of structural MRI studies in samples of antisocial populations point to abnormalities in prefrontal, limbic, temporal and subcortical areas[13–15], though evidence has been mixed and most studies have focused only on ASPD + P. A recent meta-analysis of VBM studies in ASPD + P demonstrated reliable grey matter volume abnormalities circumscribed to the left hemisphere in the dorsolateral prefrontal cortex and the medial orbitofrontal cortex[16].

Given the clinical variability within the antisocial spectrum, it is important to consider whether this may be reflected in neurobiological variability. Recent technical advances in meta-analytic techniques make quantification of variability possible, thus allowing investigation of whether the clinical variability of the disorder is reflected in parallel at a neuroanatomical level. Variability in structural imaging studies has emerged as a focus in recent meta-analyses of structural MRI studies in neuropsychiatric disorders, and these studies have found that some patient populations show greater variability in volume of certain brain regions when compared with control populations[17,18]. So far, however, this approach has not been applied to youth or adult antisocial populations. While recent meta-analyses[11,12,16] have examined volumetric differences by combining VBM studies, these are unable to quantify the magnitude of volume reductions, unable to comment on global volume differences and unable to investigate questions of volumetric variability. In this Analysis, we therefore performed a systematic review and meta-analysis of mean volume differences between individuals with DBDs, ASPD and psychopathy, and healthy controls without any mental disorder, and furthermore examined differences in brain volume variability between groups.

Results

Study selection

A total of 23 studies, reporting data from 629 antisocial individuals and 745 controls, were included (Table 1). Sufficient studies were found to conduct analyses for the following regions: total brain, total grey matter, total white matter, cerebral spinal fluid (CSF), frontal, temporal and parietal lobes, cerebellum, lateral ventricles, caudate nucleus, amygdala and hippocampus. Mean (standard deviation) age was 24.04 years (9.12 years) for antisocial participants and 24.42 years (8.26 years) for controls. Mean intelligence quotient (IQ) (standard deviation) was 95.8 (9.2) for antisocial participants and 103.4 (22.9) for controls. The antisocial groups consisted of 89.9% males, and the non-offender group consisted of 88% males.

Variability

There was significantly increased variability in antisocial individuals compared with healthy controls for total grey matter volume (log coefficient of variation ratio (lnCVR), 0.23; 95% confidence interval (CI) 0.02 to 0.43, $P = 0.029$; Fig. 1); lnCVR was not significantly different between groups for any other regions (Supplementary Fig. 1a–k). Results for lnVr (log coefficient of variation ratio) were consistent with these findings other than significantly reduced variability in antisocial individuals compared with healthy controls for amygdala (lnVR −0.24; 95% CI −0.44 to 0.04, $P = 0.02$; Supplementary Figs. 2a–k and 3a–k). Publication bias and heterogeneity (between-study inconsistency) in lnCVR for individual regions are shown in Fig. 1.

Meta-regressions for variability. A higher control:patient IQ ratio was associated with reduced lnCVR for the whole brain (that is, lower brain variability in patients) ($Z = -2.6581$, $P = 0.0079$; also lnVR, see 'Meta-regressions for variability—lnVR' in Supplementary Information). Age and ethnicity were not associated with variability (lnCVR or lnVR) differences for any region, and there were insufficient studies including female participants for the planned meta-regression of sex. As magnet strength may affect group differences[19], we also performed meta-regressions for magnet strength as a continuous variable. There were sufficient studies (≥3) for whole brain, grey matter, white matter, intracranial and amygdala. These analyses revealed no association between magnet strength and lnCVR in any region.

Mean differences

We found significant overall decreases in mean volume in antisocial groups compared with healthy controls for total whole brain ($g = -0.41$; 95% CI −0.67 to −0.15, $P = 0.0016$), total grey matter ($g = -0.6$; 95% CI −0.93 to −0.26, $P = 0.004$) and amygdala ($g = -0.89$; 95% CI −1.55 to −0.22, $P = 0.009$) (Fig. 2). There were no significant group differences for any of the other regions investigated (Fig. 2 and Supplementary Fig. 4a–k). Publication bias and heterogeneity (between-study inconsistency) for individual regions are also reported in Fig. 2.

Meta-regressions for mean differences. Age, ethnicity, IQ or magnet strength were not associated with regional mean volume differences. There were insufficient studies involving female samples to allow for our planned meta-regression based on sex.

Discussion

In this first synthesis of volumetric structural imaging data in groups of antisocial individuals to examine variability as well as magnitude, we identified significantly increased variability in antisocial individuals compared with healthy controls for total grey matter. In addition,

Table 1 | Included studies and their characteristics

Author, year	Study			Participant characteristics					Scanning properties		
	Participant groups	Diagnostic groups	*N*	Ethnicity (% non-white)	Mean age (years)	Male (%): female (%)	IQ	Offending behaviours	Scanner type	Tracing	Brain volumes studied
Barkataki et al. (2006)[86]	2	ASPD	13	–	31.6	100:0	94.2	Mixed	1.5T	Manual	Whole brain, amygdala, caudate, cerebellum, hippocampus, lateral ventricle, putamen, thalamus
		HCA	15	–	32.1	100:0	104.3	Non-offender			
Boccardi et al. (2013)[87]	2	ASPD+P	26	–	N/S	100:0	94.7	Violent	1.0T	Manual	Intracranial, accumbens, caudate nucleus, hippocampus, putamen
		HCA	25	–	N/S	100:0	N/S	Non-offender			
Budhiraja et al. (2017)[88]	2	CDA	31	–	24.1	0	N/S	Mixed	3.0T	Manual	Intracranial, white matter, grey matter, CSF
		HCA	24	–	22.7	0	N/S	Non-offender			
Dolan et al. (2002)[89]	2	ASPD+P	18	–	30.4	100:0	106.8	Violent	0.5T	Manual	Whole brain, frontal lobe, third ventricle
		HCA	19	–	30.5	100:0	113.52	Non-offender			
Glenn et al. (2010, a)[90]	2	ASPD+P	24	54%	32.7	100:0	107.5	Violent	1.5T	Manual	Anterior cingulate cortex
		HCA	24	50%	29.2	100:0	113.3	Non-offender			
Glenn et al. (2010, b)[51]	2	ASPD+P	22	54%	31.1	100:0	N/S	Not specified	1.5T	Manual	Striatum (as one measure)
		HCA	22	54%	31.0	100:0	N/S	Not specified			
Huebner et al. (2008)[91]	2	CDY	23	0%	14.5	100:0	96.7	Non-offender	1.5T	N/S	Whole brain, white matter, grey matter, CSF
		HCY	23	0%	14.2	100:0	98.9	Non-offender			
[a]Ibrahim et al. (2021)[92]	2	DBD	58	26%	11.9	100:0	N/S	Non-offender	1.0T	Freesurfer segmentation	Intracranial, white matter, grey matter, amygdala
		HCY	30	30%	12.2	100:0	N/S	Non-offender			
[a]Ibrahim et al. (2021)[92]	2	DBD	30	37%	11.3	0:100	N/S	Non-offender	1.0T	Freesurfer segmentation	Intracranial, white matter, grey matter, amygdala
		HCY	20	30%	12.5	0:100	N/S	Non-offender			
Kaya et al. (2020)[93]	2	ASPD	20	–	31.4	100:0	N/S	N/S	1.5T	Manual	Amygdala, hippocampus
		HCA	20	–	30.2	100:0	N/S	N/S			
Kruesi et al. (2004)[94]	2	CDY	10	–	16	N/S	101.7	N/S	1.5T	N/S	Whole brain, white matter, grey matter
		HCY	10	–	15.9	N/S	132.6	N/S			
Kumari et al. (2013)[95]	2	ASPD	14	–	33.5	100:0	96.35	Violent	1.5T	Manual	Anterior cingulate cortex
		HCA	15	–	32.1	100:0	106.87	Non-offender			
Laakso et al. (2002)[96]	2	ASPD	33	–	34	100:0	N/S	Violent	1.0T	Magic View 100	Frontal lobe,
		HCA	24	–	31	100:0	N/S	Non-offender			
Narayan et al. (2007)[97]	4	ASPD	14	–	33.5	100:0	N/S	Violent	1.5T	Manual	Whole brain, white matter, grey matter, CSF
		[b]SCZ (VO)	12	–	34.4	100:0	N/S	Violent			
		[b]SCZ	15	–	34.5	100:0	N/S	Non-offender			
		HCA	15	–	32.1	100:0	N/S	Non-offender			
Noordermeer et al. (2017)[98]	2	ADHD+DBD	67	0%	16.3	61:39	98	Non-offender	1.5T	Freesurfer Segmentation	White matter, grey matter, amygdala, nucleus accumbens, caudate nucleus, cerebellum, corpus callosum, hippocampus, insula, globus pallidum, parahippocampal region, putamen, thalamus
		HCY	233	0%	32.1	61:39	105.9	Non-offender			
Raine et al. (2000)[38]	2	ASPD	21	67%	31.9	100:0	98.4	Mixed	1.5T	Manual	White matter, grey matter
		HCA	34	44%	30.4	100:0	100.9	Mixed			
Raine et al. (2003)[37]	2	ASPD+P	15	67%	31.6	100:0	97.7	N/S	1.5T	Manual	White matter
		HCA	15	44%	28.8	100:0	101.6	N/S			

https://doi.org/10.1038/s44220-023-00032-0

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Table 1 (continued) | Included studies and their characteristics

Author, year	Study				Participant characteristics				Scanning properties		
	Participant groups	Diagnostic groups	*N*	Ethnicity (% non-white)	Mean age (years)	Male (%): female (%)	IQ	Offending behaviours	Scanner type	Tracing	Brain volumes studied
Sebastian et al. (2016)[99]	3	DBD+CU	29	25%	14.3	100:0	97.9	N/S	1.5T	Automatic volume	Whole brain, white matter, grey matter, CSF
		DBD−CU	31	36%	14.1	100:0	104	N/S			
		HCY	29	20%	13.6	100:0	105	Non-offender			
Tiihonen et al. (2008)[100]	2	ASPD	26	0%	34.6	100:0	N/S	Non-offender	1.0T	Automatic volume	Intracranial, cerebellum, frontal lobe, occipital lobe, parietal lobe
		HCA	25	0%	32.5	100:0	N/S	Violent			
Vetter et al. (2020)[101]	2	DBD	26		12.9	100:0	106	Not specified	3T	Freesurfer segmentation	Intracranial, grey matter, cerebellum
		HCY	30		13.5	100:0	110	Non-offender			
Wallace et al. (2014)[102]	2	DBD	22	72%	15	100:0	94.05	N/S	1.5T	Freesurfer segmentation	Amygdala, caudate, globus pallidum, putamen
		HCY	27	58%	14.9	100:0	110.96	N/S			
Yang et al. (2005)[36]	3	ASPD+P	16	69%	33.8	100:0	96.4	N/S	1.5T	Manual	Grey matter
		ASPD−P	13	47%	29.6	100:0	99.1	N/S			
		HCA	23	58%	28.3	100:0	105.1	N/S			
Yang et al. (2009)[35]	2	ASPD+P	27	56%	32.2	87:13	98.11	Mixed	1.5T	Manual	Amygdala
		HCA	32	57%	30.8	87:13	108.34	Mixed			

ASPD, antisocial personality disorder (that is, where psychopathy not specified); ASPD+P, antisocial personality disorder with psychopathy; ASPD−P, antisocial personality disorder without psychopathy; CDA, conduct disorder in (young) adult; CDY, conduct disorder youth; DBD, disruptive behaviour disorder (that is, where callous–unemotional traits not specified); DBD+CU, disruptive behaviour disorder with callous–unemotional traits; DBD−CU, disruptive behaviour disorder without callous–unemotional traits not specified; HCA, healthy control adult; HCY, healthy control youth; Mixed, sample contained both offenders and controls; N/S, not specified; VO, violent offenders (that is, where DBD/ASPD/psychopathy not specified). [a]This was a single published study; however for the purpose of our analyses, we separated into male and female samples. [b]These groups were included in the individual study but were not included in our meta-analysis.

we found significant overall decreases in mean volume in antisocial groups compared with healthy controls for total whole brain, total grey matter and amygdala.

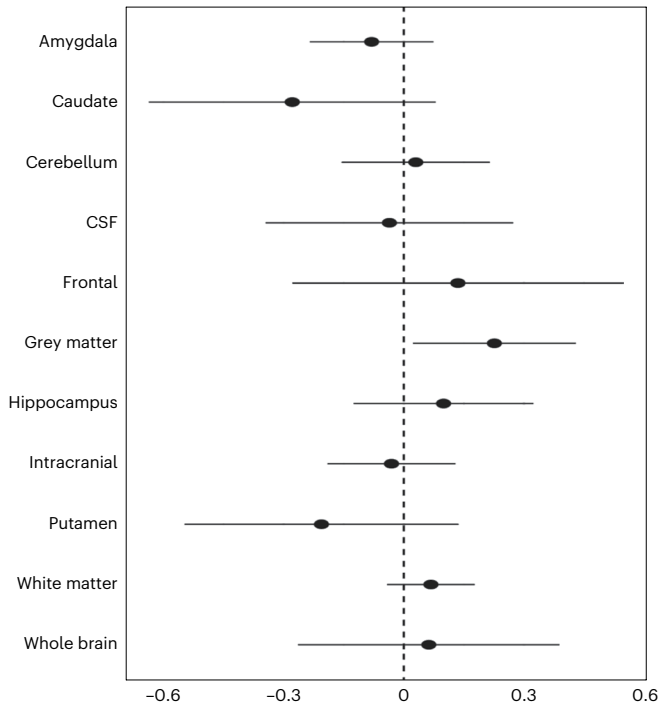
Our findings represent the first evidence for increased variability in grey matter volumes in antisocial groups, compared with healthy controls. Antisocial groups are clinically heterogeneous; for example, youth with early-onset conduct disorder (who typically display higher levels of CU traits) may have more pronounced decision-making deficits than those with later-onset conduct disorder[20] (though see ref. [21]), and conduct-disordered boys with high levels of CU traits demonstrate impaired affective empathy compared with those with low levels of CU traits[22]. In adults, studies directly comparing ASPD + P and ASPD − P are limited. However, meta-analytic studies of facial emotion recognition suggest more pronounced deficits in those with ASPD + P than in non-psychopathic offenders (most of whom meet ASPD − P criteria[23,24]). While a single previous structural imaging study has suggested that such heterogeneity may be reflected at the structural level in adults with ASPD − P versus ASPD + P[25], the current analysis is the first to address this question in an unbiased manner at the meta-analytic level. Our finding of increased variability in antisocial groups suggests neurobiological heterogeneity, which needs to be further explored.

One potential explanation for increased variability is patient groups including a mix of individuals with of DBD − CU and ASPD − P with DBD + CU and ASPD + P. Future studies would benefit from investigating whether the examination of clinical subgroups in isolation eliminates the observed increased variability in antisocial individuals. Another potential explanation is variability in pathways of structural brain development *within* antisocial groups. Put simply, different structural abnormalities compared with healthy populations may emerge due to differential mechanisms. So far, genetic and neurodevelopmental mechanisms of antisocial behaviour remain poorly understood, though genome-wide association studies have begun to identify some potential contributory factors[26–28]. One factor that may play a role in variability is relative contribution to brain volume of surface area and cortical thickness, which have been shown to have separable genetic underpinnings[29] and which contribute to the neurodevelopment of volume in autism in unique ways[30,31].

A further potential source of variability is inconsistency in phenotyping. This is a potential limitation of neurocognitive studies of DBDs and ASPD ± psychopathy, where different measurements of these constructs are often used. To limit this factor, in our study, we included only studies that categorized samples using standardized assessments for DBD, ASPD and/or Psychopathy Checklist: Revised (PCL-R)/Psychopathy Checklist: Screening Version (PCL-SV) scores for assessment of psychopathy, albeit resulting in the omission of samples of violent individuals that probably included individuals with these disorders[32–34]. We also distinguished between those with ASPD with psychopathy (ASPD + P) and those with ASPD without psychopathy (ASPD − P) when this was possible, by use of PCL-R; however, this was not used in every study of ASPD. Hence, some samples of ASPD may have included subgroups of both ASPD + P and ASPD − P, but we could not investigate to what degree presence or absence of psychopathy contributed to variability, or to what degree variability within these subgroups was significant. Other studies[35–38] included control samples with PCL-R scores above those that would be expected in the normal healthy population, and so potentially introduced further phenotypic inconsistency into our analyses. As outlined in a recent review[39], future studies will benefit from a consistent approach to defining antisocial groups and subgroups, to maximize the impact of pooled data from studies in these difficult-to-recruit populations.

It is notable that group differences in variability were identified only for total grey matter. This may be due in part to deficits in the available literature. For instance, there was an unfortunate lack of studies identified for the insula, which has been implicated in dysregulated fear conditioning[40], reinforcement learning[41], impaired

https://doi.org/10.1038/s44220-023-00032-0



K	*n*	lnCVR	95% CI	*P*	Egger's test for publication bias (*Z*)	*P*	Heterogeneity (I^2)
7	427	−0.09	−0.23, 0.07	0.30	−1.9386	0.0526	23.1%
4	379	−0.28	−0.64, 0.08	0.20	−1.4592	0.1445	73.3%
4	435	−0.03	−0.16, 0.21	0.75	0.6068	0.5440	47.1%
4	247	0.04	−0.35, 0.27	0.81	2.5377	0.0112	55.5%
3	108	0.14	−0.28, 0.55	0.52	−1.3218	0.1862	66.2%
11	868	0.23	0.02, 0.43	0.029*	−1.6633	0.096	74.6%
4	419	0.1	−0.13, 0.32	0.38	−1.0264	0.3047	24.4%
6	214	−0.03	−0.19, 0.13	0.07	1.5508	0.121	26.1%
4	379	−0.21	−0.55, 0.14	0.23	−1.6030	0.1089	80.1%
10	800	−0.07	−0.04, 0.18	0.22	−1.3831	−0.1666	0%
6	276	−0.06	−0.26, 0.39	0.806	−2.9372	0.0033	82.9%

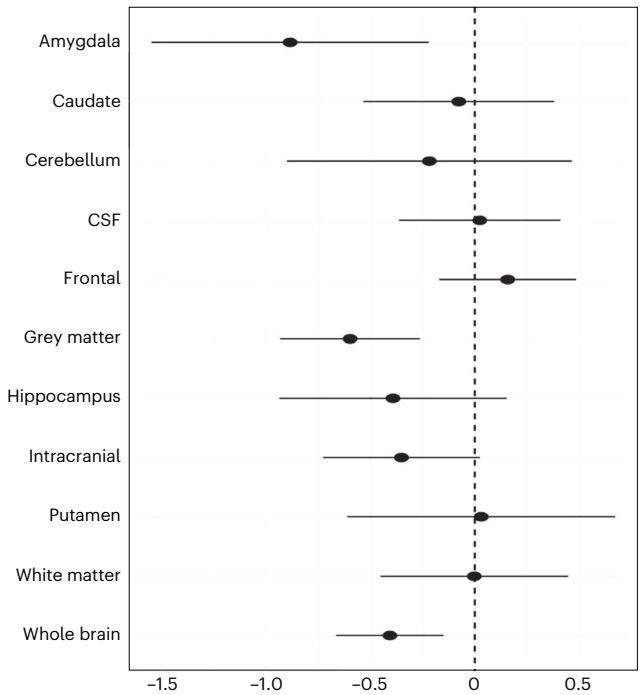
Fig. 1 | Forest plot of variability (CVR) by region. Results of a two-sided random effects meta-analysis. Data are presented as lnCVR values ± 95% CI. Total brain volume (TBV) is calculated as a sum of the grey and white matter volumes. Intracranial volume (ICV) is calculated as a sum of the TBV and the CSF volumes. *K* indicates number of studies, and *n* indicates total number of participants in all included studies. *Significant at $P < 0.05$ level.

processing of facial emotions[42], and abnormal cognitive[43] and emotional[44] empathic responding. Further, there were insufficient studies to examine variability specifically within subregions of the prefrontal cortex, for example, ventromedial prefrontal cortex (vmPFC), which has been identified as a key component of both empathic processing[45,46] and decision-making[47,48] networks. Although we included subregions of striatum in our analysis, there was a relative dearth of studies, meaning important differences in variability between groups may have been undetected. Abnormalities in striatal structure and function have been reported in a number of antisocial populations, including children with psychopathic traits[49], adolescents with conduct disorder[50], and adults with ASPD + P[51], and may be particularly important to neuropsychological function in these groups. Specifically, striatum probably has a central role in network-level modulation of decision-making, as demonstrated by numerous prior studies in animals and humans[52,53], and meta-analyses also suggest reduced striatal activity during emotion processing in antisocial youth[11,54]. Our review included caudate and putamen; however, it did not include the nucleus accumbens, an important part of the ventral striatum that has a role in guiding action selection and cost/benefit decision-making[55]. Given the potential importance of variability within each of these regions, future work will benefit from inclusion of a wider range and more granular investigation of structural differences in antisocial groups. It is of interest that there was a suggestion of *reduced* variability in antisocial groups in the amygdala. This was based on a secondary measure of variability (lnVR). If this finding is confirmed in future studies, it suggests this may be a region of consistently affected core pathology in ASPD, similarly to how the anterior cingulate has been identified as a core region of pathology in schizophrenia[17].

The lack of variability in white matter warrants consideration. Studies in both youth and adult antisocial populations have demonstrated deficits in white matter connectivity compared with healthy controls. One model[56] proposes a 'dual-network' pattern of abnormalities in psychopathy, with Factor 2 PCL-R (antisocial lifestyle) traits associated with abnormalities in the microstructure of a ventral 'temporo-amygala-orbitofrontal' network, connected by the uncinate fasciculus[57] and Factor 1 PCL-R (interpersonal and affective deficits) in psychopathy associated with abnormalities in the dorsal 'default-mode' network[56]. Importantly, these studies have used diffusion tensor imaging, rather than MRI, and it is does not follow that relevant deficits in white matter microstructure would be paralleled by structural integrity deficits detectable by MRI. Our findings suggest that variability in macro-structure of white matter within antisocial groups does not play a role in the clinical variability within these groups. Future studies would benefit from appraising variability within both micro- and macro-structure of white matter in antisocial populations.

The group differences in mean volumes in whole brain, total grey matter and amygdala are broadly consistent with previous structural MRI literature in groups of antisocial youth and adults. Previous meta-analyses of VBM structural MRI studies have demonstrated consistent reductions in grey matter volume across several cortical and subcortical regions, including the amygdala, in youths with DBD[11,12] and reduced grey matter volume in dorsolateral prefrontal cortex and the medial orbitofrontal cortex in adults with psychopathy[16]. These findings are in keeping with functional neural processing abnormalities in antisocial groups identified in functional MRI studies. For instance, relative to healthy youth, youth with DBDs demonstrate reduced activation in regions including vmPFC, anterior cingulate cortex, medial prefrontal cortex and ventral striatum to a range of empathy-eliciting stimuli[54], reduced amygdala responsivity specifically to fearful[58–61] and sad[62] expressions, and reduced neural responsiveness to reward within striatum and vmPFC[63–66]. Studies demonstrating

https://doi.org/10.1038/s44220-023-00032-0



K	*n*	SMD	95% CI	*P*	Egger's test for publication bias (*Z*)	*P*	Heterogeneity (I^2)
6	427	−0.89	−1.55 −0.22	0.009*	−1.7003	0.0891	91.7%
4	379	−0.08	−0.53, 0.08	0.742	−0.6385	0.5231	69%
4	435	−0.22	−0.90, 0.47	0.531	−0.8951	0.3707	89.7%
4	247	0.02	−0.36, 0.341	0.904	0.0340	0.9729	47.7%
3	108	0.16	−0.17, 0.49	0.344	−0.7318	0.4643	0%
11	868	−0.6	−0.93, −0.26	0.0004**	−1.6407	0.1009	82.7%
4	419	−0.39	−0.94, 0.15	0.158	−1.0498	0.2938	76.3%
6	214	-0.35	−0.73, −0.002	0.066	−0.4607	0.6450	70.5%
4	379	−0.03	−0.61, 0.467	0.924	z0.5592	0.5760	84.1%
10	800	0.0	−0.45, 0.45	0.991	0.1489	0.8816	87.1%
6	276	−0.41	−0.67, −0.15	0.0016*	−1.4426	0.1491	78.2%

Fig. 2 | Forest plot of mean difference by region. Results of a two-sided random effects meta-analysis. Data are presented as SMD (standardised mean difference) values ± 95% CI. Total brain volume (TBV) is calculated as the sum of the grey and white matter volumes. Intracranial volume (ICV) is calculated as a sum of the TBV and CSF volumes. *K* indicates the number of studies, and *n* indicates the total number of participants in all included studies. *Significant at $P < 0.05$ level; **significant at $P < 0.001$ level.

functional deficits in antisocial adults have focused mostly on ASPD + P. These deficits include impaired reinforcement learning, related to irregular posterior cingulate reactivity[41] and vmPFC–striatal connectivity[67]; impaired moral reasoning, related to vmPFC hypoactivity[68]; impaired processing of others' emotional faces, related to amygdala hyporeactivity[42,69]; and of others' pain, related to abnormal responsivity of the 'pain processing network' (including vmPFC, orbitofrontal cortex and insula[70]). Taken alongside this functional MRI literature, our findings suggest that structural abnormalities may underpin the functional deficits in regions responsible for both top-down (for example, prefrontal cortex) and bottom-up (for example, amygdala) social cognitive processes in antisocial individuals. Although there were a relatively small number of studies included in meta-regression based on age, participant age was found not to be a significant contributor to findings, broadly supporting a neurodevelopmental model of transition from youth DBD into adult ASPD[71].

A further important consideration is the influence of IQ. IQ has been demonstrated to be significantly correlated with grey and white matter volumes in healthy youth[72] and a developmental shift from a negative to positive correlation between intelligence and cortical thickness from early to late childhood[73]. In a nationwide (UK Biobank) sample, the association between total brain volume and general factor of intelligence ('*g*', which is closely correlated with IQ), was $r = 0.276$, with largest regional correlates including frontotemporal and occipital cortices[74]. The importance of covarying, or ideally, matching, for IQ in studies of antisocial populations has been discussed elsewhere[75]. In brief, not doing so means that IQ, and not any aspect of antisocial personality, may be driving structural brain differences between groups, undermining study findings. In our analysis, we found that IQ was not significantly associated with mean total or regional brain volumes, across the overall sample. IQ was, however, negatively associated with variability (both lnCVR and lnVR). Within-group analysis confirmed an effect of IQ on variability in antisocial individuals; however, despite this, an independent effect of group remained. These findings confirm the importance of accounting for IQ in studies of structural brain volume, but also bolster the case for an independent effect of antisocial group membership on increased variability in brain structure. Finally, the problems introduced in MRI studies by head motion artefacts also warrant consideration. Individuals with DBD/ASPD/psychopathy are more impulsive than healthy controls, and such impulsivity has been positively correlated with head movement in the scanner[76]. While there are several different approaches to deal with the resulting artefacts, these can introduce systematic bias. For instance, it has been demonstrated that head motion during MRI acquisition reduces grey matter volume estimates[77]. This issue remains pertinent despite ongoing attempts to minimize the impact of motion on data quality[78–80].

Strengths and limitations

This is the first meta-analytic study to examine variability of brain volume differences between healthy controls and antisocial populations across youth and adult samples. In addition, this is the first meta-analysis to investigate mean volume differences across all regions of the brain. Previous meta-analyses of brain structural studies in antisocial groups[11,12,16] have been limited to VBM studies, which are unable to examine variability and unable to quantify the magnitude of group differences. The lack of support for structural abnormalities corresponding to functional deficits identified in previous work, for example in striatum, insula and vmPFC, suggests the existing evidence from volumetric structural studies in antisocial groups may be insufficient to identify the full range of neural architecture involved. However, it is also possible that (1) there are more subtle structural alterations that were not identified given limitations of methodology and sample size and/or (2) some functional aberrations may relate to functional dynamics that either do not have a localized structural cause, or relate

to a distal structural abnormality. It should be noted that, apart from the difference in volume of the amygdala, which approached a large effect, all differences found were small effect sizes, which gives reason for caution in interpreting these findings. Further, the lack of studies that separated antisocial samples into groups with and without CU traits or with and without psychopathy prevented us from conducting an important proposed analysis—that is, whether or not individuals with DBD − CU and ASPD − CU have shared or distinct structural brain deficits to individuals with DBD + CU and ASPD + P. Hence, while our findings demonstrate clear evidence of increased variability at the neurobiological level, further work is required to determine if this linearly maps to clinical antisocial phenotypes.

Conclusions

In the first such analysis in antisocial populations, we found evidence that there is greater variability in the total grey matter volumes compared with healthy controls. This finding suggests that there is a heterogeneity in the neurobiological underpinnings of antisocial behaviour. Further work should seek to identify how this neurobiological variability maps to clinical variability and in addition whether this holds potential value as a biomarker to guide prognosis or treatment selection.

Methods

The protocol for this study was pre-registered with PROSPERO, ID number CRD42021250980, registered 25 June 2021

Study selection

A comprehensive search was conducted of PubMed, EMBASE, Web of Science, Scopus and PsycINFO from inception to 31 January 2022. Search terms used to identify the studies were '((magnetic resonance imaging' or MRI) AND (volume OR SBM OR seed OR morphology OR morphometry OR (gray OR grey) OR cortical OR anatomy OR structur* OR brain) AND (violen* OR offend* OR antisocial OR prisoner* OR (dissocial personality disorder) OR psychopath*) OR (disruptive behaviour disorder OR disruptive behavior disorder) OR (conduct disorder) OR (oppositional defiant disorder)). We supplemented the search by manual and bibliographic cross referencing, and by examining previous systematic reviews and meta-analyses[11–13,16] to identify potentially missed studies (for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart, see Supplementary Fig. 1). Studies were initially included if they were (1) published as a peer-reviewed article with original data and reported measures of total and/or regional brain volumes; (2) included individuals with DBD (± CU traits) or ASPD (± psychopathy), defined using standardized classificatory tools (Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria for DBDs and ASPD, PCL-R or PCL-SV for psychopathy) and a healthy control group; (3) had sufficient data to extract mean and standard deviations, or *t* or *P* values, for both groups; and (4) were written in English. Studies were excluded if they were done in individuals without the above diagnoses, or if they specifically investigated comorbidity (for example, schizophrenia + ASPD) where all patient groups displayed comorbidity. Studies were tabulated using a Google Doc Excel spreadsheet, to facilitate further screening of eligibility. Due to the level of overlap of symptoms between attention-deficit hyperactivity disorder (ADHD) and antisocial conditions and offenders, we included antisocial and offender samples with ADHD. As substance misuse disorders are exceptionally common in antisocial conditions, we included antisocial samples with substance misuse disorders. We did not include samples consisting wholly of individuals with substance misuse disorders as controls; however, samples with very low levels of substance misuse disorder (less than 10%) were included as controls, if not excluded for other reasons. If samples overlapped across papers, we included only the study with the largest participant size. However, if the smaller studies included regions that were not covered in the larger studies, these duplicate samples remained included for the missing regions, but weighted by the smaller participant number. The search, screening and data extraction were completed independently by three separate researchers: J.T., B.C. and B.G. Measures reported by subgroups (for example male versus female) were included as separate results. Where studies presented left and right hemisphere volumes separately, these were combined to a single measure, as previously described[81], using correlation coefficients derived from an existing dataset (Supplementary Table 1). Means and standard deviations of volumetric measures for both antisocial individuals and non-offender groups were extracted. Brain structures were included in the analysis if at least three studies met the inclusion criteria. We recorded details of the potential moderating factors of age, sex, ethnicity and IQ. Two reviewers (J.T. and B.C.) assessed the quality of each study using a modified version of the Newcastle–Ottawa Scale for case–control studies (in which the exposure category is not considered due to its lack of relevance for imaging studies). Each study received a score from zero (low quality, high risk of bias) to six stars (high quality, low risk of bias). A threshold of ≥4 stars was used to designate a high-quality study (see 'Risk of bias/quality assessment' in Supplementary Information).

Outcome measures for variability

We measured the relative variability of brain regions in antisocial individuals compared with controls, by using the log variability ratio (lnVR):

$$\ln \mathrm{VR} = \ln\left(\frac{\sigma_\mathrm{p}}{\sigma_\mathrm{c}}\right) = \ln\left(\frac{S_\mathrm{p}}{S_\mathrm{c}}\right) + \frac{1}{2\left(n_\mathrm{p}-1\right)} - \frac{1}{2(n_\mathrm{c}-1)}$$

where σ_p and σ_c are unbiased estimates of population standard deviations for antisocial individuals and controls, respectively, S_p and S_c are reported samples standard deviations, and n_p and n_c are the sample sizes.

As variance is often positively correlated with mean, between-group difference in variability are possibly in part driven by between-group differences in the mean. Hence, for our primary outcome we used the lnCVR, which accounts for differences in mean:

$$\ln \mathrm{CVR} = \ln\left(\frac{\sigma/\bar{x}_\mathrm{p}}{\sigma_\mathrm{c}/\bar{x}_\mathrm{c}}\right) = \ln\left(\frac{S_\mathrm{p}/\bar{x}_\mathrm{p}}{S_\mathrm{c}/\bar{x}_\mathrm{c}}\right) + \frac{1}{2\left(n_\mathrm{p}-1\right)} - \frac{1}{2(n_\mathrm{c}-1)}$$

where x_p and x_c are the reported means for antisocial individuals and controls. Where lnCVR (or lnVR) is 0, equal variability between antisocial individuals and controls is found, whereas >0 indicates greater variability in the antisocial individuals group compared with the controls, and <0 indicates lower variability in the antisocial individuals group.

Outcome measures for mean differences

Between-group differences in mean volumes were quantified using standardized mean difference (Hedges' *g* (refs. [82,83])). This allows for comparison of effect sizes between imaging studies that do not report raw volume differences. The typical interpretation of Hedges' *g*, as for Cohen's *d*, is as follows: 0.2, small effect; 0.5, medium effect; 0.8, large effect[84].

Meta-analyses

All analyses were conducted using the metafor package in R (3.0-2). In both the meta-analysis of standardized mean differences and that of variability, individual study effect sizes were entered into a random effects meta-analytic model using restricted maximum likelihood estimation. Separate meta-analyses were conducted for each brain region. Meta-analysis was only performed if at least three eligible studies were available. Egger's test, funnel plots and trim-and-fill analyses were conducted to test for publication bias in cases where there were at least ten studies, and the I^2 statistic was used to quantify between study inconsistency.

Meta-regressions

To examine the effects of moderating factors on mean differences and variability, we employed separate meta-regressions of sex (male or female), age, ethnicity and IQ as moderators for the mean volume differences and variability. For age, we used the mean age of the sample as the covariate of interest. For ethnicity, due to limited data provided across studies, we used the categories white and non-white and used the proportion of non-white as the covariate of interest. For IQ, to examine whether group differences may in part reflected in IQ differences between controls and antisocial individuals, a meta-regression was performed using ratio of mean non-offender:mean antisocial IQ scores as the covariate.

A significance level of $P < 0.05$ (two-tailed) was used for all analyses. Extracted data from papers and analytical code used are available on request from the authors.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Analysis data are available at https://github.com/JohnTullyPsych/AntisocialStructuralVariabilityMeta ref. [85], and data sources are all listed in AntisocialStructuralVariabilityMeta_Excel.csv.

Code availability

Analysis code is available at https://github.com/JohnTullyPsych/AntisocialStructuralVariabilityMeta ref. [85], and code sources are all listed in AntisocialStructuralVariabilityMeta_Excel.csv.

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Acknowledgements

R.A.M.'s work is funded by a Wellcome Clinical Research Career Development Fellowship (224625/Z/21/Z). None of the other authors received funding towards this work.

Author contributions

J.T. and R.A.M. conceived the idea. J.T., B.C. and B.G. performed the literature search and cross-checking of papers. J.T. performed the analyses, with input from R.A.M. J.T. wrote the initial draft. J.T., B.C., B.G., J.G., N.B., R.J.B. and R.A.M. all provided critical analysis on scientific content on this and further drafts.

Competing interests

R.A.M. has received honoraria for educational talks from Otsuka and Janssen. None of the other authors has any conflict of interest, financial or otherwise, to disclose.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s44220-023-00032-0.

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Peer review information *Nature Mental Health* thanks Nathaniel Anderson, Olivia Choy and Natalia Tesli for their contribution to the peer review of this work.

https://doi.org/10.1038/s44220-023-00032-0

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Diffusion MRI ☐ Used ☐ Not used

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