Brain Structural Correlates of Irritability: Findings in a Large Healthy Cohort

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Abstract: Irritability and nonviolent aggression are common behavioral features across the population, yet there is limited neurobiological research into subclinical phenotypes representing the lower edge of a symptom continuum ranging from slight irritability to criminal violence. We studied brain structural correlates of irritability in a large healthy cohort to test the hypothesis of associations with fronto-limbic brain structures implicated in mood regulation. In a large multicenter effort, we recruited 409 mentally healthy adults from the community, who received T1-weighted high-resolution 3 T MRI scans. These structural scans were automatically preprocessed for voxel- and surface-based morphometry measurements with the CAT 12 toolbox implemented in SPM 12. Subclinical aggressive symptoms were assessed using the SCL-90-R aggression/hostility subscale and then correlated with cortical volume (VBM), and cortical thickness and gyrification. VBM analysis showed significant ($P < 0.05$, FDR-corrected at peak-level) positive correlations of cortical volume with SCL-90-R aggression subscale values in large clusters spanning bilateral anterior cingulate and orbitofrontal cortices and left lingual and postcentral gyri. Surface-based morphometry yielded mostly uncorrected positive correlations with cortical thickness in bilateral precentral gyri and with gyrification in left insula and superior temporal gyrus. Our findings imply an association of subclinical aggressive symptoms with cortical volume in areas important for emotion awareness and regulation, which might also be related to cortical adaptation to mental stress. These results overlap

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with several findings on impulsive aggression in patients suffering from affective and disruptive behavior disorders. They also suggest a biological symptom continuum manifesting in these brain areas. *Hum Brain Mapp 00:000–000, 2017.*

Key words: VBM; cortical thickness; gyrification; subclinical aggression; healthy subjects

INTRODUCTION

Aggression spans a large variation of cognitions, emotions, and behaviors—ranging from slight irritability, bad temper, to frankly violent behavior [Blair, 2016; Rosell and Siever, 2015]. This broad phenotype therefore includes clinical symptoms not only in the affective disorder spectrum and disruptive behavior disorders [Baker et al., 2015], antisocial behavior, and violent criminal deviance across multiple psychiatric conditions [Bertsch et al., 2013], but also in nonclinical populations of any age. Physical violence being a major public health issue, there has been a great effort to understand neurobiology of aggression so far [Nelson and Trainor, 2007]. Beside the distinction between impulsive and instrumental aggression, current concepts distinguish between reactive and proactive aggression [Baker et al., 2008; Bushman and Anderson, 2001; Fung et al., 2009]. Possibly due to reasons of experimental practicability, most studies focused on reactive, impulsive aggression, mainly in psychiatric patients with different diagnoses or in normal development in healthy children and adolescents [Antonucci et al., 2006; Gansler et al., 2009]. So far much valuable information about the neurobiological features of aggressive behavior in these groups has been acquired [Peper et al., 2015; Rosell and Siever, 2015].

Several studies robustly point to the central role of amygdala, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC), and the connections between them to modulate aggressive behaviors [Blair, 2016; Leibenluft, 2017; Raschle et al., 2015; Rosell and Siever, 2015]. Many of these studies have relied on clinical samples (especially antisocial disorders, conduct disorders, and affective disorders) or have focused on developmental aspects across childhood and adolescence [Baker et al., 2015; Boes et al., 2008; Sterzer and Stadler, 2009; Waller et al., 2017]. In contrast, there are only few structural imaging studies that have studied aggression in adult nonclinical samples.

In youths/adolescent clinical samples such as disruptive behavior disorders, aggression and antisocial behavior have repeatedly been associated with reduced gray matter in orbitofrontal and insular cortices, and amygdala (for review, see Baker et al. [2015]), and thinning in anterior cingulate cortices [Fahim et al., 2011]. In contrast, boys with callous-unemotional conduct had higher grey-matter density in anterior cingulate and medial orbitofrontal cortices when compared with normally developing boys, which was interpreted as an indicator of delayed development [De Brito et al., 2009]. Orbitofrontal cortical thickness in children with attention-deficit hyperactivity disorder (ADHD) has also been reported to correlate with higher aggression, but not impulsivity [Cha et al., 2015]. Orbitofrontal and ventromedial prefrontal cortex, and frontal and temporal poles also show volume alterations in different groups of adult violent offenders depending on their personality structure [Bertsch et al., 2013]. Studies in children and adolescents have also suggested a modulating effect of gender on the association between right ACC and aggression, pointing to a particular effect in aggressive boys [Boes et al., 2008], and similar effects (in ACC and gender interactions) in healthy male adolescents [Visser et al., 2014]. There is also evidence for a negative correlation of aggression and amygdala volume from a large cohort children study [Thijssen et al., 2015], and a similar effect has been shown in healthy adults [Matthies et al., 2012; Pardini et al., 2014]. The co-variance pattern of amygdala volume and (global) cortical thickness in children, adolescents, and young adults has been shown to correlate with aggression, and this effect was mediated by testosterone [Nguyen et al., 2016]. Finally, there is also some emerging evidence from a recent study of adolescent twins that proactive and reactive aggression is associated with striatal enlargement [Yang et al., 2016], which also implicates part of the basal ganglia in aggression [Haber, 2003].

The studies, mostly using voxel-based morphometry (VBM), have partially been supported by diffusion tensor imaging (DTI) analyses of structural connectivity of white matter. A recent review of studies on antisocial behavior indicates that such aggressive behavior is associated with increased diffusivity in the uncinate fasciculus, a tract connecting (inferior) frontal with temporal brain areas and thus an important fronto-limbic pathway [Waller et al., 2017]. A study in healthy young adults, however, failed to show an association with OFC–amygdala connectivity to be related to trait aggression [Beyer et al., 2014]. A larger study spanning subjects age 8–25 did, in fact, show a correlation of impaired widespread fronto-subcortical and fronto-temporal connectivity, and this effect was modulated by testosterone [Peper et al., 2015].

While the above studies indicate structural associations of aggression with brain regions including the amygdala, ACC, OFC, and insula, there is little data (a) in adult populations, and (b) nonclinical samples. In this study, we used both voxel-based and surface-based morphometry to address this issue and test the hypothesis of an association with aggression/irritability in healthy adult nonclinical community samples. In particular, we hypothesized a correlation of self-report aggression/hostility with grey matter in the ACC, OFC, insula, and amygdala. We tested

TABLE I. Epidemiologic data on the three subsamples

	Jena-1 ($n = 177$)	Jena-2 ($n = 141$)	Milano ($n = 91$)
Mean age (SD)	29.8 (± 8.93)	32.12 (± 14.27)	29.13 (± 7.7)
Age range	20–60	19–73	18–62
Gender	83 f, 94 m	87 f, 54 m	55 f, 36 m
Mean IQ (SD)	106.23 (± 11.5)	115.87 (± 14.81)	122.39 (± 8.49)
Mean SCL-90-R aggr/host scale value (SD)	0.27 (± 0.35)	0.24 (± 0.4)	0.21 (± 0.3)
SCL-90-R aggr/host range	0–2.17	0–3.5	0–1.5

Overview of age, gender, IQ, and SCL90-R aggression subscale values given as mean and standard deviation (SD). f, female; m, male.

this hypothesis using both voxel-based morphometry (VBM) and surface-based measures of cortical thickness and gyrification.

METHODS

Participants

We included 409 healthy young adults (mean age 30.45, SD 10.9, range 18–73, 225 f, 184 m) consisting of three subsamples. The participants were recruited as healthy controls for ongoing case–control studies in Jena, Germany, and Milano, Italy. The Jena-1 sample consisted of 177 persons, while the Jena-2 sample consisted of 141 persons scanned later on the scanner following an extensive hardware and software upgrade, which led us to treat these two subject groups as separate samples. The Milano sample consisted of 91 persons. An overview of demographic data of the three samples is given in Table I.

The 318 participants recruited in Jena gave written informed consent to a study protocol approved by the local Ethics Committee of Jena University Medical School, while the 91 participants recruited in Milano provided written informed consent to a study protocol approved by the Ethics Committee of the Azienda Ospedaliera Universitaria of Verona.

None of the participants had a present or history of DSM-IV axis I disorders, as determined by careful screening via phone (Jena samples) resp. by a modified interview derived from the SCID-IV nonpatient version (SCID-NP) (Milano sample). They also had no history of major neurological and unmedicated internal medical conditions, and psychiatric history in first-degree relatives.

In the Jena samples, we used the MWT-B, a German language inventory similar to the NART [Antretter et al., 2013], to estimate IQ and confirm the inclusion criterion of IQ higher than 80. All Milano participants met this criterion, but IQ was estimated using the Italian version of the Wechsler Adult Intelligence Scale–Revised [Orsini and Laicardi, 2000; Wechsler, 1981].

To assess subclinical occurrence of aggressive symptoms, subjects completed SCL-90-R around the time of scanning. The SCL-90-R is a well-established self-rating instrument to assess a broad range of psychopathological symptoms and is a commonly used tool for the assessment of psychological distress across multiple symptom domains [Derogatis et al., 1976]. It is among the most widely used self-rating instruments with more than 1000 published studies in various clinical and nonclinical settings [Tarescavage and Ben-Porath, 2014]. The SCL-90-R consists of 90 items, each to be rated on a 0–4 Likert-type scale, which can then be analyzed syndrome-wise with nine different scales. The participants are asked to rate the symptoms according to their occurrence during the last 7 days. We selected scale 6 summarizing symptoms of aggression/hostility within 6 items (feeling easily annoyed or irritable, having uncontrolled temper outbursts, urges to harm someone, urges to break things, frequent arguments and shouting, and throwing things). Dividing the cumulating value of the scale by the number of items, we calculated the scale value, which could therefore rank from 0 to 4.

Within the three samples, there was no significant correlation of SCL-90-R aggression/hostility subscale values with age, gender, or IQ (two-tailed Pearson correlations, each with $P > 0.1$). There was also no significant difference of SCL-90-R aggression subscale values between male and female participants (ANOVA, $P > 0.1$).

Magnetic Resonance Imaging (MRI)

Subjects for the Jena-1 sample underwent high-resolution T1-weighted MRI on a 3 T Siemens Tim Trio scanner (Siemens, Erlangen, Germany) using a standard quadrature head coil and an axial three-dimensional magnetization prepared rapid gradient echo (MP-RAGE) sequence (TR 2,300 ms, TE 3.03 ms, α 9°, 192 contiguous sagittal slices, FoV 256 mm, voxel resolution $1 \times 1 \times 1$ mm^3; acquisition time 5:21 min).

Participants of the Jena-2 sample were scanned on a Siemens Prisma fit system (Siemens, Erlangen, Germany), which was based on the above Siemens Tim Trio scanner, after undergoing a significant upgrade (both hardware and software). The structural scan was acquired with an MP-RAGE sequence with similar parameters (TR 2,300 ms, TE 2.07 ms, α 9°, 192 contiguous sagittal slices, FoV 256 mm, voxel resolution $1 \times 1 \times 1$ mm^3; acquisition time 5:21 min) as part of a 25 min imaging session.

Milano MRI scans were acquired with a 3T Magnetom Allegra Syngo MR 2004A (Siemens, Erlangen, Germany) also using a standard head coil for radiofrequency transmission and reception of the MRI signal. An MP-RAGE

sequence was acquired (TR 2,060 ms, TE 3.93 ms, α 15°, 160 contiguous sagittal slices, FoV 256 mm, voxel resolution 1 × 1 × 1 mm^3, acquisition time 7:32 min). The scan was part of an MRI protocol of total duration of about 50 min.

Voxel-Based Morphometry

We used the CAT 12 toolbox (Computational Anatomy Toolbox 12) of the Structural Brain Mapping group, Jena University Hospital, Jena, Germany, which is implemented in SPM12 (Statistical Parametric Mapping, Institute of Neurology, London, UK) for voxel-based morphometry (VBM) analysis of imaging data. All T1-weighted images were corrected for bias-field inhomogeneities, then segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) [Ashburner and Friston, 2005] and spatially normalized using the DARTEL algorithm [Ashburner, 2007]. The segmentation process was further extended by accounting for partial volume effects [Tohka et al., 2004], applying adaptive maximum *a posteriori* estimations [Rajapakse et al., 1997]. After preprocessing and in addition to visual checks for artefacts, all scans passed an automated quality check protocol. Scans were smoothed with a Gaussian kernel of 8 mm (FWHM). For exclusion of artefacts on the grey-/white-matter border (i.e., incorrect voxel classification), we applied an absolute grey-matter threshold of 0.1. Owing to the involvement of amygdala in impulsivity and aggressive behavior, we performed additional small-volume corrections for bilateral amygdala applying a region of interest derived from the SPM Neuromorphometrics atlas (in DARTEL space).

Surface-Based Morphometry: Cortical Thickness and Gyrification

For surface-based morphometry (SBM), we used the surface-preprocessing pipeline of the CAT 12 toolbox. We used a projection-based thickness estimation that allows calculating cortical thickness and the central surface in one step [Dahnke et al., 2013]. This method also includes partial volume correction and correction for sulcal blurring and sulcal asymmetries. Topological correction is performed through an approach based on spherical harmonics. For reparametrization of the surfaces, an algorithm for spherical mapping of the cortical surface with reduced local distortions is applied [Yotter et al., 2011]. An adapted two-dimensional diffeomorphic DARTEL algorithm was then applied to the surface for spherical registration.

The gyrification index can be extracted based on an absolute mean curvature approach [Luders et al., 2006]. Central cortical surfaces were created for both hemispheres separately. Finally, all surface measures were resampled and smoothed with a Gaussian kernel of 15 mm (FWHM).

Statistics

For statistical comparison, we applied the general linear model (GLM) approach implemented in SPM12. We performed one GLM each correlating SCL-90-R aggression subscale values with GMV, cortical thickness, and gyrification. For VBM analysis, we included total intracranial volume (TIV) as a nuisance variable to remove the related variance. We performed whole-brain analyses investigating both positive and negative correlations between scale value and anatomical marker. Scanner was added as a factor to remove all variance related to the different acquisition sites/subsamples, across all analyses.

RESULTS

Voxel-Based Morphometry (VBM) Analysis

Our VBM analysis showed large clusters with a positive correlation of cortical volume with SCL-90-R aggression/hostility subscale values mostly across bilateral anterior cingulate and orbitofrontal cortices and gyrus rectus and left lingual and postcentral gyri ($P < 0.05$, FDR-corrected at peak level). An overview is given in Table II. We did not find any negative correlations. Also small-volume correction for bilateral amygdala did not reveal any significant correlations with SCL90-R aggression subscale (Fig. 1).

In addition to our main analyses, we also explored the potential interactions of aggression with gender and testing for age effects. For that purpose, we added (in those analyses showing significant main effects of a structure-aggression correlation) an interaction of aggression levels by gender, and also a correlation with age.

We found a significant ($P < 0.05$, FDR corrected) interaction of aggression × gender, with higher correlations in males across multiple areas, including the orbitofrontal cortex (mostly left), left superior temporal cortex/Rolandic operculum, bilateral precuneus and right cuneus, right insular cortex, a cluster including left precentral and postcentral cortices, right transverse temporal cortex, and left cerebellum. However, there were no clusters showing an interaction with higher correlation in women than men. Also, there was no significant interaction of age with aggression scores.

Surface-Based Morphometry (SBM): Cortical Thickness and Gyrification

We found cortical thickness to be positively correlated with SCL-90-R aggression/hostility scores bilaterally in postcentral gyrus and two smaller left-hemispheric clusters. These results did not survive correction for multiple comparisons except for the right-hemispheric postcentral cluster ($P < 0.05$, FWE-corrected at cluster level) (Table III and Fig. 2). Atlas labeling was performed according to Desikan–Killiany atlas [Desikan et al., 2006].

For cortical gyrification, we found one left-hemispheric and one right-hemispheric cluster, in which gyrification

TABLE II. VBM: results of the correlation with SCL90-R aggression subscale

Anatomical area	Co-ordinates of peak-voxel	Cluster size (*k*)	*P* (FDR-corrected at peak-level)	*T*
Left Rolandic operculum and postcentral gyrus	−50; −8; 14	172	0.041	4.81
Left lingual gyrus	−14; −81; −3	243	0.041	4.7
Left sup. (med.) frontal, anterior	−14; 39; 24	643	0.041	4.32
and middle cingulate gyri	−9; 34; 40			4.32
	−4; 39; 34			4.09
Right anterior cingulate cortex and OFC	8; 30; −3	179	0.041	4.32
Bilat. gyrus rectus and OFC	0; 15; −22	171	0.041	4.1
	3; 8; −20		0.048	3.61
Left paracentral lobule and postcentral gyrus	−10; −36; 75	123	0.041	4.07
	−21; −32; 69		0.049	3.57
Left anterior cingulate gyrus	−2; 44; 8	76	0.041	3.97

Overview of clusters of significant positive correlation of grey-matter volume with SCL90-R aggression subscale values showing anatomical label, co-ordinates of peak-voxel, cluster size (expected voxels per cluster $k = 68$), and *P*- and *T*- values ($P < 0.05$, FDR-corrected at peak level).

was positively correlated with aggression values (Table IV and Fig. 3) at uncorrected thresholds ($P < 0.001$). No negative correlations were found for surface-based measures.

DISCUSSION

In a multicenter dataset of nonclinical psychiatrically healthy volunteers, we identified a positive correlation of self-reported aggression (irritability and hostility) and grey-matter volume (VBM) in bilateral anterior cingulate and orbitofrontal cortices and gyrus rectus and left lingual and postcentral gyri. Findings derived from surface-based morphometry measures mostly did not show comparably strong results, in particular not holding for correction for multiple comparisons.

Several of the anatomical regions found in our VBM analyses have been implicated in the processing and regulation of affect and emotion, including the broad spectrum of anger, hostility, and aggression.

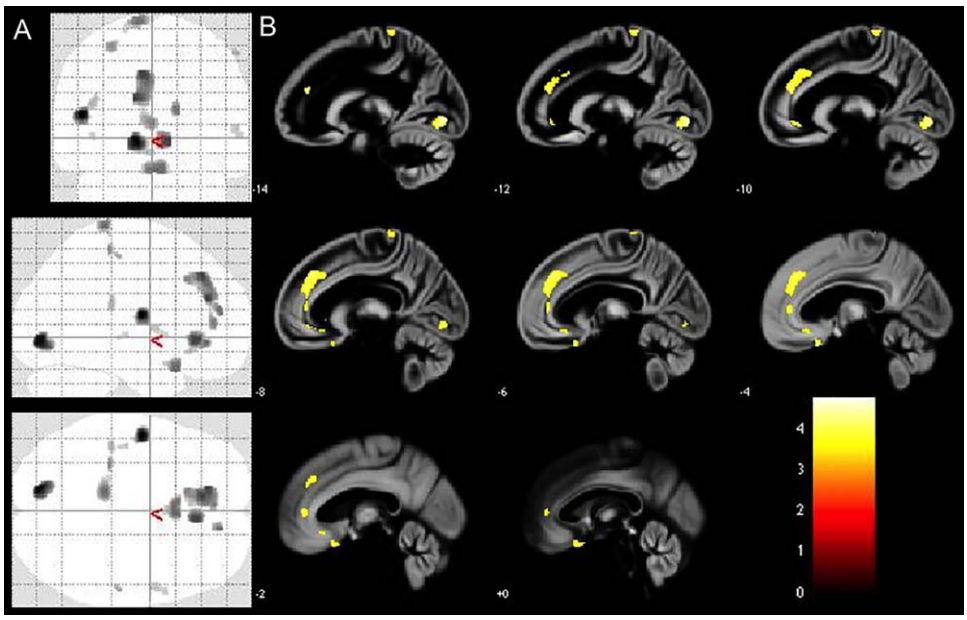

Figure 1.

Clusters of significant positive correlation of cortical volume with SCL90-R aggression subscale values ($P < 0.05$, FDR-corrected at peak level), shown as (**A**) maximum intensity projection and (**B**) slice overlay on an average image calculated from grey-matter maps of overall participants. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Cortical thickness: results of the correlation with SCL90-R aggression subscale

Overlap of atlas region	Cluster size	*P* (uncorrected)	*T*
99% left postcentral	347	0.00033	3.43
55% left lateraloccipital	62	0.00047	3.33
45% left inferior temporal			
72% right postcentral	590	0.031*	3.67
28% right precentral			
100% postcentral	116	0.00051	3.31

Overview of clusters of significant positive correlation of cortical thickness with SCL90-R aggression subscale showing atlas regions, cluster size, *P*, and *T* values.
*FWE-corrected at cluster level.

The anterior cingulate cortex is (together with OFC) one of the prefrontal limbic structures central to the integration of affective, sensory, and cognitive processes to determine an appropriate yet flexible response [Rudebeck and Murray, 2014; Walton et al., 2007]. In large cohorts of healthy children and adolescents, reduced right ACC volumes have been associated with increased aggressive and defiant behavior [Boes et al., 2008]. Consistent with its role in emotion processing, ACC shows various structural alterations and functional impairment in both unipolar [Alexopoulos et al., 2008; Lichenstein et al., 2016] and bipolar depression [Blumberg et al., 2000; Fountoulakis et al., 2008]. Also subclinical depressive symptoms in older adults were positively correlated to ACC volume in different subregions of the cingulate [McLaren et al., 2016].

The positive correlation of ACC volume and aggression in our samples of healthy adult nonclinical subjects contrasts with the mostly negative correlation in (mostly clinical) child and adolescent samples [Baker et al., 2015; Boes et al., 2008]. An explanation for these divergent findings might be that these structures see considerable structural changes across development in adolescence in early adulthood and therefore associations in children or adults might reflect delayed cortical maturation [De Brito et al., 2009], while this association changes in adulthood. Our interaction analysis of aggression by gender, while showing that gender (especially male subjects) indeed seem to drive several of the associations, this effect did not show in the ACC. Together with the lack of significant age effects, our ACC finding does indeed implicate ACC structure to be associated with aggression/hostility in nonclinical adults.

Another major area of interest for aggression is the orbitofrontal cortex. Together with the amygdala, these two brain structures are essential for threat perception [Li, 2014]. Only a couple of studies showed OFC volume alterations associated with life-time aggression in a mixed psychiatric population with psychotic subjects ($n = 41$) compared to healthy controls [Gansler et al., 2009] and without psychotic subjects ($n = 15$) [Antonucci et al., 2006]. To our knowledge, there are no adult nonclinical structural neuroimaging studies in humans demonstrating an association between aggression and structure of primary olfactory cortex so far.

In contrast to our results, many studies in smaller cohorts of healthy persons found smaller amygdala volumes correlated with higher levels of aggression in men and women and with clinical relevant and "normal" levels of aggression [Matthies et al., 2012; Pardini et al., 2014]. This association, however, did not take into account psychopathy. A recent study also found lower amygdala volume in nonpsychotic violent control subjects [Del Bene et al., 2016]. Further studies in clinical and nonclinical samples investigated anatomical subdivisions of the amygdala and hemispheric features.

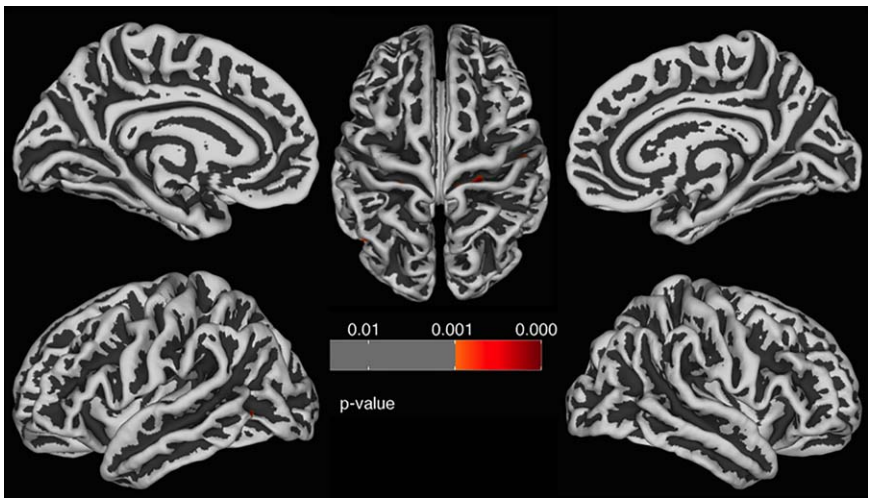

Figure 2.
Clusters of significant positive correlation of cortical thickness with SCL90-R aggression subscale values ($P < 0.001$, uncorrected at peak level). The underlying surface is the average central surface. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE IV. Cortical gyrification: results of the correlation with SCL90-R aggression subscale

Overlap of atlas region	Cluster size	*P* (uncorrected)	*T*
79% left insula	354	0.00001	4.44
21% left superior temporal gyrus		0.018*	
100% left lateral occipital gyrus	36	0.00052	3.3
100% left caudal middle frontal gyrus	18	0.00065	3.24
100% right caudal middle frontal gyrus	77	0.00014	3.71

Overview of clusters of significant positive correlation of cortical gyrification with SCL90-R aggression subscale showing atlas regions, cluster size, *P*, and *T* values.
*FWE-corrected at cluster level.

Especially the left dorsal amygdala seems to be of particular relevance [Bobes et al., 2013; Gopal et al., 2013], although functional significance is not yet clear. The role of amygdala subdivisions and possibly opposite volume changes due to symptoms of aggression or even subclinical affective symptoms could be a reason why the area did not show any changes in our sample.

Finally, there is also growing evidence of the involvement of the striatum in mediation of aggressive behavior [Haber, 2003]. The insight comes from a functional study, reporting striatal activation during responses to fairness and retaliation, strongly modulated by serotonin [Crockett et al., 2013]. Striatal enlargement is correlated with both reactive and proactive aggression in adolescent twins [Yang et al., 2016]. We did not find any structural associations in our study, possibly due to the low levels of aggression in our sample.

In contrast to VBM findings, we did not find a robust effect on cortical thickness. Although cortical thickness is closely related to grey-matter values derived from VBM and these two measures often correlate, they do not show complete overlap. The two methods detect similar, but somewhat divergent properties of brain tissue and might diverge in sensitivity to detect minor structural variations. In contrast, cortical folding is thought to reflect morphological properties related to brain development, as it is determined during the first months of life and correlates with early developmental deviations [Zilles et al., 2013]. It might thus be less prone to change during transient expression of a phenotype. Our negative findings for gyrification are therefore indicative of a lack of a substantial effect of early brain development on later liability to show irritable, hostile, or frankly aggressive behavior in subclinical ranges.

We need to consider some limitations of our study. First, our study was cross-sectional, which limits several interpretations, especially on the temporal stability of aggression/hostility in healthy subjects. Longitudinal studies would be helpful to address not only changes in trait markers, but also the hypothesis that some (prefrontal) areas might show late maturation well into early adulthood, and that this might interact with levels of aggression. Second, our interpretation of VBM vs gyrification findings, although supported by the literature on early brain development, is limited by the lack of longitudinal studies on gyrification and its temporal stability. Third, we cannot exclude the emergence of subthreshold or manifest psychopathology is some of our subjects at later stages. Also, it is not clear how resilience to stress might interact with factors to modulate the levels of aggression in nonclinical subjects. Finally, different studies have used

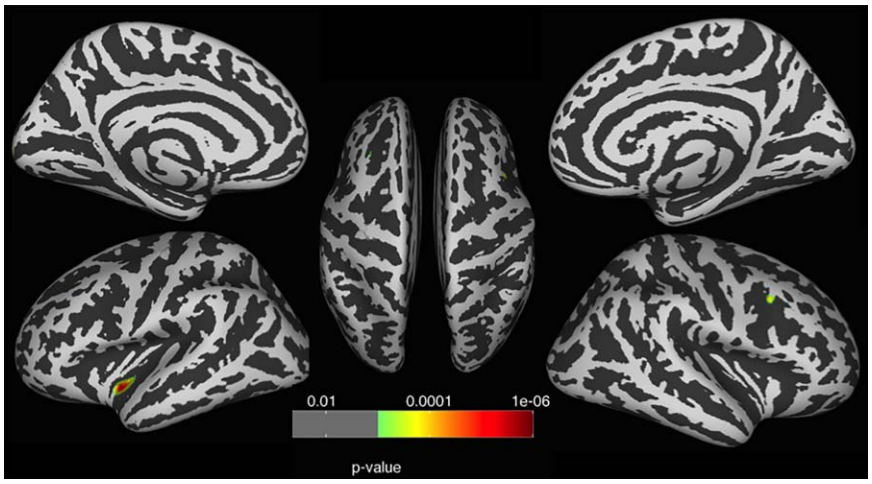

Figure 3.
Clusters of significant positive correlation of cortical gyrification with SCL90-R aggression subscale values ($P < 0.001$, uncorrected at peak level). The underlying surface is the inflated average surface. [Color figure can be viewed at wileyonlinelibrary.com]

different measures of aggression/hostility, so even each of these might have demonstrated validity, they might capture slightly different facets of aggressive behaviors.

Taken together, we show a robust association of nonclinical variation in "every-day" aggressive phenotypes of healthy volunteers with cortical volume in important areas for emotion perception and processing, especially, the anterior cingulate and orbitofrontal cortices. These correspond to several findings on impulsive aggression but also in psychiatric patients suffering from affective disorders. Our results thus lend support to a biological continuum model of a broad aggression phenotype, which is associated with some of the brain structures also identified in clinical conditions. Further studies are needed to explore whether the findings might reflect adaptations to higher levels of mental stress. To confirm this assumption, further studies in healthy samples with longitudinal and additional functional measurements would be helpful.

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CONFLICTS OF INTEREST

The authors declared that they have no conflicts of interest with the content of this article.

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