Caudate Gray Matter Volume in Obsessive-Compulsive Disorder Is Influenced by Adverse Childhood Experiences and Ongoing Drug Treatment

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Background: Exposure to adverse childhood experiences (ACE) increases the risk of adult physical and mental health disorders, including obsessive-compulsive disorder (OCD), and influences adult cortical neural responses and gray matter (GM) volumes. Robust neuroimaging findings associated OCD with corticostriatal dysfunction and with abnormal morphology and metabolism of cortical areas and basal ganglia.
Methods: We explored the GM correlates of ACE in 40 patients with OCD (15 drug-naive and 25 drug-treated patients) with magnetic resonance imaging voxel-based morphometry at 3.0 T. Regional GM volumes were the dependent variable, and drug treatment (naive vs treated) and breadth of exposure to ACE (high vs low) were the factors of interest. Sex, duration of illness, and handedness were considered as nuisance covariates. Whole brain statistical threshold was $P < 0.05$ familywise error corrected for multiple comparisons.
Results: Patients with higher levels of exposure to ACE showed increased GM volume in the head of the left caudate nucleus. Ongoing drug treatment was associated with reduced GM volume in the same area. Earlier age at onset of OCD, need for medication treatment, and mixed handedness were correlated with higher levels of ACE.
Conclusions: Exposure to ACE increased, and ongoing drug treatment decreased, caudate GM in OCD. Increased volume and metabolism of the caudate nucleus have been consistently associated with OCD. Our findings suggest a detrimental effect of ACE on the brain underpinnings of OCD, with an opposite effect of medications.

Key Words: obsessive-compulsive disorder, caudate nucleus, antiobsessive medication, childhood trauma, handedness

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Current views on the pathogenesis of psychiatric disorders focus on the interplay between genetic and environmental factors, with individual variation in vulnerability and resilience to hazards being part of the multifactorial development of illness.[1] Environmentally mediated causal risk processes include the effects of early psychosocial adversities,[2] which have been associated with poorer emotional and physical functioning and with higher vulnerability to further trauma exposure.[3] Given that adaptive systems can resist or recover from marked disturbances when they are healthy and functional, it is hypothesized that vulnerability and resilience in psychiatry could be mediated by changes in neural circuits involving many neurotransmitter and molecular pathways, and shaping the individual differences in coping with stress.[4]

Recent brain imaging studies confirmed the possibility to explore in adult life the persistent neural correlates of adverse childhood experiences (ACE). Among healthy humans, the offspring of families marked by harsh parenting with overt family conflict and deficient nurturing ("risky families" [RF]) had higher activation of prefrontal cortex and reduced activation of limbic structures in response to an emotional task.[5] Our group confirmed the functional effects of ACE in corticolimbic structures of both healthy and schizophrenic subjects and showed that differences in neural responses are paralleled by differences of gray matter (GM) volumes.[6]

The relationship between breadth of exposure to early stress and later occurrence of psychiatric disorders[7] has been extended to mood disorders, anxiety disorders, and schizophrenia.[1,8] A sparse but consistent literature associated childhood emotional and physical abuse and neglect with the diagnosis of obsessive-compulsive disorder (OCD),[9,10] with the dimensions of OCD psychopathology,[11,12] and with OC symptoms in the general population.[13]

Neuroimaging findings in OCD are among the most robust reported in the psychiatric literature,[14] but no study explored the brain correlates of ACE in patients with OCD. Following the earlier line of reasoning, we studied the possible effects of ACE on the brain GM morphometry of adult patients with OCD.

MATERIALS AND METHODS

Sample, Treatment, and Clinical Assessment

We studied 40 patients (26 males and 14 females) affected by OCD (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, *Structured Clinical Interview for DSM-IV* interview) and consecutively referred to our hospital unit. Fifteen patients were drug naive, and 25 were being administered a drug treatment upon clinical need (clomipramine, n = 10; fluvoxamine, n = 9; sertraline, n = 1; all patients were taking benzodiazepines).

Severity of ACE was rated on the Risky Families Questionnaire (RFQ)[5] by summing the scores obtained on each of the 13 items (with each score ranging from 1 to 5) to obtain a global score. The RFQ has been adapted from an instrument originally developed to assess the relation of family stress to mental and physical health outcomes in adulthood.[7] Previous research validated this questionnaire against clinical interviews conducted and coded by trained clinical interviewers.[15] In the absence of validated cutoff values to discriminate higher and lower levels of ACE, the median of the distribution was calculated and participants were divided into "high RF" or "low RF" based on

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their RFQ score being greater or less than the median score. This approach has been proven successful in detecting the structural and functional brain correlates of ACE in adult life.[5,6]

Severity of symptoms was rated on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).[16] Handedness was assessed with the Edinburgh inventory.[17]

After complete description of the study to the subjects, a written informed consent was obtained. The local ethical committee approved the study protocol.

Image Acquisition and Analysis

Morphometric magnetic resonance image scanning took place in the afternoon. Structural magnetic resonance imaging scan for the analysis of voxel-based morphometry (VBM) was acquired on a 3.0-T scanner (Gyroscan Intera, Philips, the Netherlands) using a 6-channel SENSE head coil, with a T-1-weighted MPRAGE sequence (repetition time, 25.00 ms; echo time, 4.6 ms; field of view, 230 mm; matrix, 256 × 256; in-plane resolution, 0.9 × 0.9 mm, yielding 220 transversal slices with a thickness of 0.8 mm).

Images were analyzed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging Neuroscience, London, England) and the VBM toolbox implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), which combines tissue segmentation, bias correction, and spatial normalization into a unified model.[18] The procedure yielded modulated GM-normalized images: modulated parameters were used to test for voxelwise differences in the relative volume of GM by compensating for the effects of warping.[19] The voxel size for all images was resliced to 1 × 1 × 1 mm. We realigned the scans to correct for head movement. Images were normalized to the standard echo-planar image template volume of the Montreal Neurological Institute reference brain, and smoothed to an 8-mm full width at half maximum isotropic Gaussian kernel. Total intracranial volume was calculated as the sum of the volumes of GM, white matter, and cerebrospinal fluid, as estimated by the MATLAB get_totals script implemented for SPM (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).

To assess the statistical significance of group differences, data were analyzed within the context of the general linear model. Modulated images were entered into an analysis of variance for the group comparison of GM volume with 2 factors: severity of ACE (high vs low) and medication status (drug naive vs drug treated). Sex, duration of illness, handedness, and total brain volume were included in the model as nuisance covariates. The effects of the 2 factors were analyzed together in an analysis of variance design (F contrasts and conjunction analysis), and one at a time (*t* contrasts). This procedure allowed for identification of the regions where both factors significantly influenced the GM volumes (conjunction analysis, as implemented in the SPM5 statistical software package), and for testing of the levels of significance of the main effects of ACE and of drug status one by one. The analysis was performed on the whole GM, without restricting it to any region of interest. The statistical threshold was $P < 0.05$ familywise error (FWE) corrected for multiple comparison, with a minimum cluster size $k = 50$.

RESULTS

Clinical and demographic characteristics of participants and significance of the observed differences are summarized in Table 1. Drug-naive patients reported significantly lower ACE than drug-treated ones. Patients exposed to worse ACE showed earlier at onset of illness and more mixed handedness. No other difference was statistically significant.

TABLE 1. Clinical and Demographic Characteristics of Participants Divided According to Use of Medications (Drug Naive Versus Drug Treated) and Severity of ACE (High Versus Low)

	Drug-Treated Participants (n = 25)	Drug-Naive Participants (n = 15)	*t* or χ^2	*P*
Age	36.12 ± 10.82	34.4 ± 8.72	0.52	0.605
Sex	9 F, 16 M	5 F, 10 M	0.03	0.864
Years at school	12.44 ± 3.08	14 ± 3	1.56	0.126
Handedness	19.48 ± 7.15	19.27 ± 6.52	0.09	0.925
Age at onset of illness	14.48 ± 7.52	16.07 ± 6.04	0.69	0.493
Duration of illness	21.56 ± 12.07	18.4 ± 8.02	0.90	0.374
Y-BOCS score	32.96 ± 4.95	31 ± 4.53	1.25	0.219
RFQ score*	28.04 ± 9.39	21.27 ± 6.89	2.42	0.020*
	High ACE (n = 20)	**Low ACE (n = 20)**	**t or χ^2**	***P***
Age	34.15 ± 9.00	36.80 ± 11.00	0.83	0.409
Sex	7 F, 13 M	7 F, 13 M	0.00	1.00
Years at school	12.90 ± 3.28	13.15 ± 3.01	0.25	0.803
Handedness*	16.70 ± 8.48	22.10 ± 2.94	2.69	0.010*
Age at onset of illness*	11.85 ± 6.47	18.30 ± 5.99	3.27	0.002*
Duration of illness	22.35 ± 9.72	18.40 ± 11.56	1.17	0.250
Y-BOCS score	31.10 ± 4.80	33.35 ± 4.73	1.49	0.144

*$P < 0.05$.

At the VBM analysis (Fig. 1), the effects of ACE and current drug treatment survived the statistical threshold in a single cluster of 55 mm^3 in the head of the left caudate nucleus (at Montreal Neurological Institute coordinates: x = −8, y = 19, z = 3; $F_{1,32} = 17.91$, Z = 5.42, $P_{FWE} = 0.006$). Here, patients with higher ACE had increased GM volumes than patients with lower ACE ($t = 3.91$, Z = 3.52, $P_{FWE} = 0.009$), and patients taking drugs had significantly lower volumes than drug-naive patients ($t = 4.41$, Z = 3.88, P_{FWE}=0.003).

DISCUSSION

This is the first study reporting an effect of ACE and drug treatment on GM volumes in adult patients with OCD. The effect was significant in the left head of the caudate nucleus, where higher levels of ACE were associated with increased GM volumes, and ongoing drug treatment was associated with an opposite effect.

The caudate nucleus plays a crucial role in reward detection, goal representation, and goal-directed action.[20,21] A significant increase in the volume of the caudate's head has been described since the beginning of the brain imaging study of OCD,[22] and a recent meta-analysis confirmed morphometric abnormalities by showing that (*a*) patients with OCD had normal global GM volumes but increased regional GM volumes in bilateral lenticular nuclei extending to the caudate nuclei, and (*b*) more severe OCD was associated with increased GM volumes in the basal ganglia.[23]

In a lifetime perspective, ACE can increase psychiatric disability via psychosocial impairment and the adoption of health risk behaviors.[7] In light of the association of OCD with

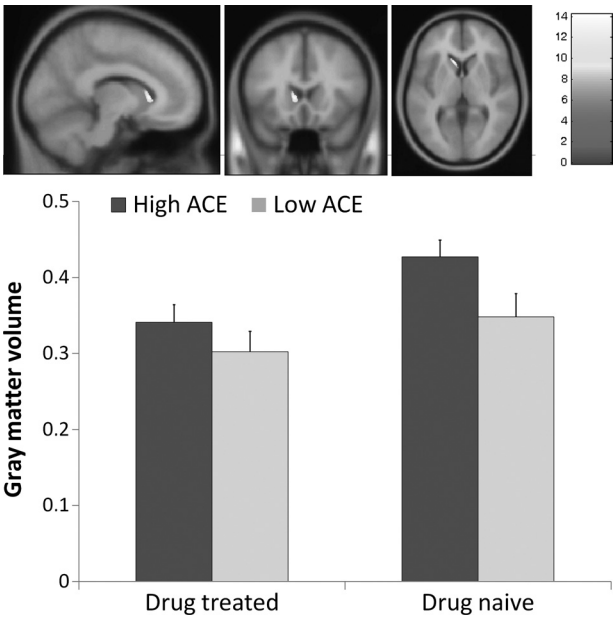

FIGURE 1. Top, Localization of the cluster where ACE and ongoing drug treatment significantly influenced GM volume (signal peak at MNI coordinates: x = −8, y = 19, z = 3). Rendering has been performed on the standard T1 MNI template. The color bar shows F values. Bottom, Direction and size effect of the significant differences: patients with higher ACE had increased GM volumes than patients with lower ACE, and patients taking drugs had significantly lower volumes than drug-naïve patients. Bars represent mean values, and whiskers represent standard errors.

increased GM volume in the caudate's head, our observation of increased GM associated with worse ACE suggests that the relationship between ACE and OCD psychopathology could be mediated by a detrimental effect of ACE on the specific biological underpinnings of OCD. We previously showed that in patients with schizophrenia, ACE are associated with GM volumes of prefrontal and cingulate cortex,[6] which are brain areas where GM volumes are influenced by the disorder.[24] It is then tempting to speculate that effects of early stressors might reveal in specific brain areas depending on possible specific biological vulnerabilities and endophenotypic markers associated with the different psychiatric disorders.

The morphological abnormalities of caudate nucleus in OCD are paralleled by abnormal functional responses[25,26] and by an increased metabolic activity, which tends to decrease and normalize with treatment.[27,28] Our observation that ongoing drug treatment is associated with reduced caudate's GM volumes suggests that these effects could be paralleled by morphometric changes and that effective treatment could counteract the detrimental effects of early stress in this area.

These interpretations are however limited by the uncontrolled nature of our study. Only prospective studies with standardized treatments will allow definite conclusions on these topics.

Higher ACE were associated with earlier age at onset, which might represent the penetrance of the system for specific genetic liability involved in the genesis of the illness[29] and for environmental hazards. The drug-naive patients reported lower ACE than the drug-treated ones, in agreement with previous reports of increased rates of psychotropic prescriptions in humans exposed to ACE.[30] Finally, higher RFQ scores were associated with more mixed handedness, suggesting interactions between hemispheric lateralization and the emotional impact of ACE in OCD. Left or mixed lateral preference has been consistently associated with greater emotional distress during exposure to traumatic events[31] and with a greater probability to develop posttraumatic stress disorder.[32,33]

Limitations of the present study, which is retrospective, uncontrolled, and correlational in nature, include issues of generalizability, previous medications, non–drug-naive patients, no placebo control, no standardized treatments, population stratification, no evaluation for compliance, varying treatment periods, without consideration of gene-environment interactions.

AUTHOR DISCLOSURE INFORMATION

FB, SP, and DR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. None of the authors have financial disclosures pertinent to the contents of the manuscript.

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