Structural Neuroimaging of Anorexia Nervosa: Future Directions in the Quest for Mechanisms Underlying Dynamic Alterations

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ABSTRACT
Anorexia nervosa (AN) is a serious eating disorder characterized by self-starvation and extreme weight loss. Pseudoatrophic brain changes are often readily visible in individual brain scans, and AN may be a valuable model disorder to study structural neuroplasticity. Structural magnetic resonance imaging studies have found reduced gray matter volume and cortical thinning in acutely underweight patients to normalize following successful treatment. However, some well-controlled studies have found regionally greater gray matter and persistence of structural alterations following long-term recovery. Findings from diffusion tensor imaging studies of white matter integrity and connectivity are also inconsistent. Furthermore, despite the severity of AN, the number of existing structural neuroimaging studies is still relatively low, and our knowledge of the underlying cellular and molecular mechanisms for macrostructural brain changes is rudimentary. We critically review the current state of structural neuroimaging in AN and discuss the potential neurobiological basis of structural brain alterations in the disorder, highlighting impediments to progress, recent developments, and promising future directions. In particular, we argue for the utility of more standardized data collection, adopting a connectomics approach to understanding brain network architecture, employing advanced magnetic resonance imaging methods that quantify biomarkers of brain tissue microstructure, integrating data from multiple imaging modalities, strategic longitudinal observation during weight restoration, and large-scale data pooling. Our overarching objective is to motivate carefully controlled research of brain structure in eating disorders, which will ultimately help predict therapeutic response and improve treatment.

Keywords: Anorexia nervosa, Connectome, Diffusion tensor imaging, Eating disorders, Magnetic resonance imaging, White matter microstructure

http://dx.doi.org/10.1016/j.biopsych.2017.08.011
situations, the primary objective of this article is to motivate well-controlled research to help predict therapeutic response and eventually improve treatment. A cornerstone of this endeavor is promoting more standardized study protocols and large-scale data pooling and encouraging future studies with advanced technologies that integrate endocrine, metabolic, and (epi)genetic biomarkers.

**STRUCTURAL NEUROIMAGING TECHNIQUES IN AN RESEARCH**

Brain imaging can evaluate the structure and function of the living brain, pointing to mechanisms related to pathophysiology. A benefit of studying brain structure is that it tends to be more stable and less dependent on acute emotional and motivational states compared with functional neuroimaging. While early computed tomography studies in AN (33) were limited in their ability to detect localized alterations, recent structural magnetic resonance imaging (MRI) studies employed more sophisticated scanning and analysis procedures.

Volumetry based on T1-weighted MRI is one of the most frequently used techniques to study brain macrostructure. The introduction of voxel-based morphometry revolutionized structural neuroimaging, as it enabled automated quantification of GM and WM density from MRI intensity gradients (11). Most studies of AN focused on cortical and/or subcortical volume (26–29). However, cortical GM volume is a composite measure comprising two independent components: cortical thickness and surface area (34). Recent AN studies evaluated cortical thickness (20,35), folding, or gyriﬁcation (36,37). Brain WM volume is often altered in psychiatric disease, including AN (28,29), but little is known about speciﬁc alterations in various disorders (38). Going beyond WM volume, several recent AN studies (39–41), including longitudinal observations (42–44), employed diffusion tensor imaging (DTI) (Supplemental Table S1), which provides information on WM integrity by quantifying water diffusivity along axons (45). The most common metric is fractional anisotropy (FA), a scalar value that describes the degree of anisotropic and/or directional diffusion associated with axon diameter, fiber packing density, membrane permeability, and myelination. FA is typically interpreted as a marker for WM integrity, but it is affected by several processes and cannot provide a deﬁnitive mechanistic explanation (46). To better characterize dynamic (pathological) microstructural abnormalities, DTI studies often include additional measures, including mean diffusivity—an overall measure of water diffusion—and measures of diffusion perpendicular or parallel to WM tracts (radial and axial diffusivity). Recent studies used DTI tractography to investigate WM fiber connectivity (25,43,47) measured by so-called streamlines that identify connection density and quality.

**Figure 1.** Rapid macrostructural brain changes in anorexia nervosa during weight restoration. Selected sagittal (top panel), coronal (middle panel) and axial (bottom panel) T1-weighted magnetic resonance images of (A) an acutely underweight adolescent patient with anorexia nervosa at admission to an inpatient eating disorder treatment (age, 15.6 years; body mass index, 16.2) and (B) the same patient 14 weeks later at discharge following weight restoration therapy (body mass index, 19.5). The images demonstrate widespread sulcal enlargement and marked ventricle dilation in illness and rapid normalization following nutritional rehabilitation. To illustrate the dynamic alteration in brain structure in anorexia nervosa objectively, this patient was chosen from the longitudinal sample from Bernardoni et al. (20) based on her standardized body mass index change score between admission and discharge, which was equal to the sample mean. Note that changes apparent in single-subject raw magnetic resonance images may not be representative of changes detected in group analyses of processed images, which may include regionally increased brain mass both in the underweight stage and after long-term recovery (22,49).
CURRENT STATE OF STRUCTURAL NEUROIMAGING RESEARCH IN AN

The increasing number of structural neuroimaging studies in AN (Figure 2) have been qualitatively reviewed and quantitatively meta-analyzed (Supplement) (26–30). The most comprehensive meta-analysis (28,29) concluded that globally reduced GM and WM volume in acutely underweight patients with AN normalizes during weight restoration, suggesting that alterations may merely reflect malnourishment. However, some well-controlled studies found larger frontal and subcortical volumes (22,39,48,49), and some regions, including cingulate gyrus (21,48,50) and cerebellum (31,32,51–53), appear to be altered more frequently than others. Furthermore, adolescents and adults may differ in the persistence and prognostic implications of structural alterations. Reports relating GM differences to clinical variables or cognitive function (19,22,32,54,55) are also heterogeneous, with AN normalizes during weight restoration, suggesting that alterations may merely re...

Figure 2. Structural magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) studies in anorexia nervosa. Graph depicts the increasing number of structural MRI and DTI studies in anorexia nervosa samples (n > 2 patients) published since the first known study in 1990 until July 2017 as identified with systematic PubMed and Scopus searches using the following terms: anorexia nervosa, eating disorders, MRI, magnetic resonance imaging, neuroimaging, DTI, diffusion tensor imaging, diffusion-weighted imaging. References for all studies counted in the graph are presented in the Supplement.
orders of magnitude faster than age-related changes (20). While interrupted in AN, but the effects of malnutrition are at least one covarying for age, others have adopted the often favorable strategy of focusing on homogeneous age ranges in separate analyses (19,22,39,41).

Figure 3. State-of-the-art structural neuroimaging research in anorexia nervosa (AN). (A) Using a connectomics approach (135,136) to compare network modularity (139) in diffusion tensor imaging data (whole-brain white matter tractography) acquired from weight-restored patients with AN (n = 24) and healthy control (HC) subjects (n = 31), Zhang et al. (60) found abnormal community structure in AN in a network composed of the caudate, pallidium, nucleus accumbens, and rostral and caudal anterior cingulate and posterior cingulate (orange regions). (B) In a longitudinal multimodal analysis (138,143) of diffusion tensor imaging and resting-state functional magnetic resonance imaging data collected in acutely underweight patients with AN (n = 22) and HC subjects (n = 18), Cha et al. (43) found increased structural connectivity, increased white matter fractional anisotropy, and increased functional connectivity as well as altered effective connectivity in a reward-related fronto-accumbal network in AN before treatment. Structural connectivity between the nucleus accumbens (NAcc) and left orbitofrontal cortex (IOFC) (top) continued to be abnormally increased relative to HC subjects following weight restoration (bottom left), and fractional anisotropy remained elevated (bottom right; red region). (C) In another multimodal analysis of diffusion tensor imaging and functional magnetic resonance imaging data during taste processing collected in acutely underweight patients with AN (n = 26), Frank et al. (47) found altered (increased and decreased) structural connectivity in food reward-regulating circuitry in patients with AN relative to HC subjects (n = 26) and an inverted pattern of effective connectivity between the hypothalamus and ventral striatum driven by the anterior cingulate. (D) In a longitudinal investigation of acutely underweight patients with AN (n = 35), Bernardoni et al. (20) found a global increase of cortical gray matter thickness (84% of the cortical surface) following brief weight restoration therapy (<3 months following admission to a specialized nutritional rehabilitation program) and relative normalization compared with both long-term weight recovered patients with AN (n = 34) and HC subjects (n = 78). The heat map depicts regions of the lateral (top) and medial (bottom) surface of the brain in both hemispheres showing significantly increased cortical thickness between baseline (within 96 hours after admission) and follow-up measurement after a minimum 10% body mass index increase. ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex.

Extraneous Variables

In addition to controlling for eating disorder–specific factors, including clinical subtype (and subtype history), age of illness onset, and illness duration, future studies should control for other potential confounds, such as comorbidity (1,5), medication (74) including oral contraceptives (75), menstrual cycle (76), physical activity (77), and, in adolescents, pubertal stage (78). For analyses, use of covariates should be kept to a minimum to avoid overfitting statistical models. Depending on specific research questions, subanalysis of the influence of variables that are present only in the clinical group is important, both within-group (e.g., duration of illness) and between-(sub)group (e.g., medication) analyses.

Enhancing Reproducibility and Generalizability

Researchers are encouraged to follow best practices in neuroimaging (79) and to take proposed guidelines (Table 1) into consideration, many of which apply generally to eating disorders.

Potential Neurobiological Mechanisms Underlying Structural Brain Alterations in AN

Alterations in brain structure may result from multiple processes, but the underlying mechanisms remain poorly understood (80). In this section, we discuss possible explanations for brain morphological changes in AN, including 1) intracellular fluid moving into extracellular spaces because of altered oncotic (colloid osmotic) pressure or dehydration (81); 2) loss of glial or neuronal cells (e.g., apoptosis); 3) macronutrient and/or micronutrient deficiency (82,83); and 4) suppression of leptin (84), reduction of gonadal and thyroid hormones as well as neurotrophins, and cortisol increase (72). The last-mentioned possibilities could contribute to inadequate protein biosynthesis, which may lead to a) changes in or loss of dendritic spines, fiber reorganization, and delayed synaptogenesis (neuronal remodeling) and b) increased lipid catabolism and/or decreased myelination and shrinkage of glial cells (glial remodeling).

Dehydration and Oncotic Pressure

As noted above, targeted studies are needed to confirm preliminary evidence indicating that dehydration may not explain...
Preliminary neuroimaging studies of AN report reduced gray matter (GM) mass in the parietal, frontal, and temporal lobes (19,20). Additional altered GM regions include the cingulated cortex, insula, and other brain areas (21,22). Additional studies have identified lower GM density in AN patients relative to controls (23). In studies of adults (24), some regions such as the putamen (25) showed significant GM reductions. A systematic review of imaging research in AN reported a GM reduction in acute AN (19,20,42). Additional measurement methods, such as bioelectrical impedance analysis (with vector analysis), may also be helpful (85). It would also be important to differentiate between hypovolemia and hypovolemia that is due to loss of electrolytes, and researchers need to take into account that hemoconcentration candidates for brain changes in AN.

Apoptosis of Brain Cells

Postmortem histological data from an AN case study suggest an abnormally slender neuron type with a long basal dendritic field and reduced spine density and/or altered spine morphology indicative of cellular degeneration (91). Animal models of AN show reduced proliferation of brain cells but not massive cell loss (92). If apoptosis were the underlying cause of GM loss in acute AN, normalization following weight restoration would be unlikely unless neurogenesis occurred. However, the rapid GM increase during therapy (roughly 4% globally in only 3 months) (20) is hardly compatible with the comparatively sluggish turnover rate documented in select neuronal subpopulations in adults (1%–2% annually) (93). Preliminary findings from studies using neuronal and glial damage and/or activation markers, such as neuron-specific enolase and glial fibrillary acid protein (GFAP) (94), speak against a massive acute loss of brain cells. However, the normal age-dependent increase in peripheral GFAP (95), which may reflect expansion of mature, differentiated astrocytes (96), is absent in acute AN. Thus, reductions in size or changes in morphology of glia or neurons and dendrites seem more likely candidates for brain changes in AN.

Dietary Intake: Macronutrients and Micronutrients

Patients with AN disproportionately avoid consuming fats (97,98). Consequently, plasma concentrations of several lipids (including essential fatty acids) are lower or altered in patients with acute (99,100) but normal in recovered patients (101). Lipids (especially cholesterol, glycerophospholipids, and sphingolipids) are major components of brain structure (102). Many fatty acids can be produced endogenously, but some polyunsaturated fatty acids that are crucial for fluidity of neuronal membranes and for modification of the number and affinity of membrane bound enzymes, receptors, and ionic channels must be provided by diet (103). Deficiency of polyunsaturated fatty acids has been associated with structural brain alterations (64), but such relationships have yet to be explored in AN.

Insufficient intake of fats and other macronutrients may also be associated with inadequate micronutrient intake. Few studies have investigated intake or plasma levels of vitamins and trace elements (including iron), but there may be a reduction of several micronutrients, especially vitamin B12 and zinc (104). Zinc deficiency has been suggested to play a causal role in AN (105), but a recent large study found reduced levels in only 3% of the adult patients, and other vitamin or mineral deficiencies were found in only approximately 45% of patients—less than expected given frequent dermatological symptoms in AN suggestive of micronutrient deficiency (106).
Similarly, iron deficiency is surprisingly uncommon in AN (107). Iron is one of the many constituents of myelin, and iron concentration is related to WM fiber integrity (108). For example, higher serum transferrin levels are associated with lower fractional anisotropy in various WM tracts (109). Although the consequences of micronutrient deficiencies on neurological function have long been known (e.g., vitamin B1 and Wernicke encephalopathy), the study of how nutrients affect brain structure is relatively new (82,83,110) and has been neglected in AN research. Because evaluating micronutrient intake using questionnaires may be unreliable (111), measuring plasma levels may be preferable.

Endocrine System

The hypothalamic-pituitary-adrenal axis is hyperactive in AN, and the “hunger hormone” ghrelin is elevated, whereas the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes and the adipocyte-derived hormone leptin is suppressed (71,72). Cortisol concentrations are elevated in AN (112), and cortisol is known to impact brain structure (113). Suppression of the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axis in AN has been attributed to restricted energy intake or increased energy expenditure and may be an adaptation to low energy availability—i.e., sexual reproduction would cost energy required for vital body functions. Beyond their role in sexual differentiation, gonadal steroids are critical for brain development, especially during adolescence (114). Estradiol, for example, protects neurons from excitotoxins and oxidative stress (115) and promotes dendritic growth, neurotransmitter synthesis, and neuronal depolarization (116). Despite endocrine dysregulation in AN, few studies have investigated relationships with brain structure. One computed tomography study (117) found associations between the width of cortical sulci and hypocortisolemia and hypogonadotropic hypogonadism, which is compatible with an MRI study reporting a link between follicle-stimulating hormone and regional GM volumes (51). Another study found an increase in global GM volume following weight recovery to correlate negatively with blood cortisol levels (54). Given established relationships between leptin and GM volume in healthy individuals (118), future studies might seek to clarify the relative contribution of leptin deficiency to structural brain anomalies in AN.

NEUROTROPHIC FACTORS

Neurotrophin brain-derived neurotrophic factor (BDNF), nerve growth factor, and glial-derived neurotrophic factor are proteins that modulate neuronal or glial development or regeneration and have been repeatedly related to brain changes. BDNF promotes the growth, differentiation, and survival of neurons (119) and plays a role in synaptic plasticity (120) as well as food intake and weight regulation (121). Reduced BDNF levels in acute AN are well established (122,123), as are variations in GM and WM morphometry as a function of BDNF polymorphisms (124). However, studies testing associations between circulating BDNF (and nerve growth factor and glial-derived neurotrophic factor) and brain structure in AN are lacking. Future studies should control for phasic effects of exercise on BDNF levels (125), as up to 70% of patients with AN report excessive exercise (126).

Glial and/or Neuronal Remodeling

Even if the factors discussed above do not cause apoptosis, they may contribute to structural brain alterations in AN by affecting the size or shape of neurons and glia. This hypothesis is supported by findings of deficits in somal size and density as well as dendritic branching and spine density of hippocampal pyramidal cells in protein-malnourished rats (127). Similarly, short apical dendrites, fewer spines, and dendritic spine abnormalities have been found in infants with severe malnutrition (128). Such mechanisms of neuronal remodeling have been demonstrated to underlie MRI-detectable brain volume increases following cognitive training in rodents (129). Thus, neuronal-glial remodeling seems to be a plausible explanation of structural brain changes in AN.

The most established animal model, the activity-based anorexia model (130,131), offers clues to specific mechanisms in AN. As noted above, one study showed decreased cell proliferation suggestive of reduced gliogenesis (92). Also in line with the glial remodeling hypothesis, another study (132) found chronically starved rats to have reduced cerebral cortex and corpus callosum volumes and a lower immunoreactive surface area for GFAP-positive astrocytes but not neurons or oligodendrocytes. Similarly, using an alternative AN rat model, acute dehydration-induced anorexia, another study found a reduced number of GFAP-positive astrocytes in the corpus callosum (133). Although most research focuses on neurons, astrocytes also regulate neuronal activity, protect against inflammation, support the blood-brain barrier, and supply energy to neurons (134). Smaller or less mature (remodeled), fewer, and less functional astrocytes may thus worsen the already precarious metabolic situation of neurons in acutely underweight patients with AN.

FUTURE DIRECTIONS OF STRUCTURAL NEUROIMAGING RESEARCH IN AN

Controlling for confounds is critical, but progress will likely be driven by exploring brain network architecture—the so-called structural connectome (135,136)—employing acquisition methods that quantify biomarkers of brain tissue microstructure (quantitative MRI [qMRI]) (137), integrating data from multiple modalities (multimodal imaging) (138) as well as longitudinal observation during weight restoration and large-scale data pooling. Conventional analytic approaches neglect the network complexity of the underlying neurocircuitry. Investigating interregional correlations of GM morphology (139) or systems-level changes in connectivity by modeling the neural network architecture of GM brain regions (nodes) highly interconnected by WM fiber bundles (edges) (135) may be a promising way to bring clarity to the diverse regional abnormalities in GM and WM integrity reported in AN. Several recent studies have adopted a connectomics approach to both DTI (Figure 3) (25,43,47,60) and functional MRI data (140,141), but we are far from a comprehensive understanding of altered connectivity in AN.

As T1-weighted MRI data are uninformative regarding underlying tissue properties and DTI data in AN are...
inconclusive (Supplemental Table S1), more sensitive measures are needed. Rapidly developing qMRI methods are promising in this respect. By decoupling different contrast mechanisms from the overall MRI signal, qMRI directly measures surrogate markers of microscopic tissue properties (137). For example, quantitative mapping of R1 (water proton relaxation rate) indexes myelination (142) and may help in understanding changes in WM volume and integrity in AN. Similarly, qMRI methods might clarify the potential contribution of hydration and/or dietary intake as noted above by assessing, for instance, water (69) and iron content (108). The only known qMRI study in AN found, in addition to both increased and decreased fractional anisotropy in a number of WM tracts, reduced R1 in several tracts, suggesting that impaired WM integrity reflects myelin loss (40).

Combining and integrating data obtained with different modalities such as qMRI and DTI (40) promises to foster a greater understanding of the underlying mechanisms of structural brain changes in AN than can be achieved using one method alone (138). For example, two recent multimodal imaging studies combining diffusion tractography and functional MRI found evidence linking alterations in WM structural connectivity and functional and effective connectivity between brain regions implicated in aberrant reward processing in AN (Figure 3) (43,47). To date, no AN studies have capitalized on the cross-information provided by integrating data from multiple modalities (e.g., GM density and WM integrity) as enabled, for instance, with joint independent component analysis (143).

Whereas the majority of previous structural neuroimaging studies in AN have been cross-sectional, a positive recent development has been the increase of longitudinal studies (20,42–44), which can be particularly informative regarding the biological mechanisms underlying morphological alterations associated with weight rehabilitation. For example, the rapid increase of cortical thickness following brief weight restoration therapy (3–4 months) speaks against hypotheses of apoptosis and neurogenesis and for a neuronal and/or glial remodeling explanation (20). Studying brain structure in AN at multiple time points during recovery is also potentially informative regarding therapeutic response, which may help find better treatments.

ADVANCING THE NEUROSCIENCE OF AN THROUGH COLLECTIVE ANALYSIS

As noted above, sample sizes in the structural neuroimaging literature on AN are typically small and do not, on their own, have adequate statistical power to answer more subtle research questions. For example, no study to date has compiled samples including individuals across the entire eating disorder spectrum to account for the transdiagnostic nature of AN and how brain structure might be related to symptom fluctuation along a restrictive–impulsive continuum or based on subtype history (4,144). Data from different studies are also often difficult to compare owing to methodological heterogeneity, but they are nonetheless invaluable because they provide clinical phenotyping. In 2009, researchers expert in large-scale neuroimaging or genetics formed a network called Enhancing Neuromaging Genetics through Meta-Analysis (ENIGMA) (http://enigma.usc.edu/) (145). ENIGMA has now pooled MRI and genome-wide genotyping data from greater than 30,000 individuals to discover more than 20 genetic loci affecting brain structure. In psychiatric disorders, ENIGMA has completed some of the largest collaborative neuroimaging studies to date including well over 3000 datasets each, with studies in progress in 18 conditions (146).

ENIGMA has used both a mega-analysis model, where all phenotypic data are analyzed at a central site, and a meta-analysis model, where analyses are run cooperatively across consortia sites with a pre-agreed protocol. For example, universal pre-processing, including quality control and analysis of T1-weighted MRI, is run locally using FreeSurfer (http://freesurfer.net/) with pre-agreed covariates. Subsequently, site-specific regression coefficients are combined and meta-analyzed, weighting the results based on the sample sizes of each contributing cohort. Once a network is established, all members can submit proposals with new research questions.

In 2016, an ENIGMA AN consortium (http://enigma.usc.edu/ongoing/enigma-anorexia/) dedicated to understanding structural brain changes in patients over the course of weight restoration and recovery was founded. While harmonizing acquisition and analysis of neuroimaging data across different scanners is generally challenging, and it is unclear, for instance, how cultural factors might influence brain structure in different AN subtypes, increased statistical power achieved by data pooling will allow for the examination of the contributing or modulating factors discussed in this review as well as the specificity of morphological alterations compared with other (eating) disorders.

The ENIGMA screen of genetic loci that affect the brain has revealed overlap between loci associated with brain morphometry and schizophrenia (147). The Psychiatric Genetics Consortium recently identified a genome-wide significant locus in AN on chromosome 12 (148). Additional analysis suggests positive genetic correlations with schizophrenia, educational achievement, and neuroticism and negative correlations with high body mass index and metabolic markers (148–150). Future studies could jointly screen the genome for loci associated with AN and brain measures, allowing, for the first time, causal inferences about brain differences related to genetic risk for AN.

CONCLUSIONS

Progress in understanding structural brain alterations in AN (and eating disorders generally) has been hindered by small sample sizes, methodological heterogeneity, and inadequate control for confounding variables (Table 1). In addition to outlining some steps future studies should take to avoid the shortcomings in the previous literature, this review focused on the largely overlooked question of what neurobiological mechanisms (e.g., glial remodeling) may underlie macro-morphological changes in AN. Recent momentum in the field, including the application of innovative technologies and advanced analysis, is encouraging. The quest to identify brain regions and biological processes involved in AN will be further expedited by collective pooling of imaging, clinical, and genetic data. Harmonized global data pooling as in ENIGMA offers a new source of power to test associations between brain measures, treatments, and outcomes and to establish the reproducibility and generality of findings, which is especially important in a severe illness such as AN with low prevalence.
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ACKNOWLEDGMENTS AND DISCLOSURES
This work was supported by the Deutsche Forschungsgemeinschaft Grant Nos. EH 367/5 and SFB 940 (to JAK and SE), Swiss Anorexia Nervosa Foundation (SE), Roland Ernst Stiftung (SE), National Institute of Mental Health Grant Nos. MH096777 and MH103436 (to GKWF), National Institutes of Health Grant No. EB020403 (to PMT and ENIGMA Consortium), National Institutes of Health Big Data to Knowledge program (PMT and ENIGMA Consortium), Kavli Foundation (PMT and ENIGMA Consortium), and other private and federal funders worldwide (PMT and ENIGMA Consortium).

We thank Simone Schöps, Arne Doose, and Wibke Naumann for their assistance.

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Mar 9, 2017; revised Jul 21, 2017; accepted Aug 14, 2017.

Supplementary material cited in this article is available online at http://dx.doi.org/10.1016/j.biopsych.2017.08.011.

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