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Structural brain correlates of interpersonal violence: Systematic review and voxel-based meta-analysis of neuroimaging studies

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ABSTRACT

Owing to inconsistent nomenclature and results, we have undertaken a label-based review and anatomical likelihood estimation (ALE) meta-analysis of studies measuring the quantitative association between regional grey matter (GM) volume and interpersonal violence. Following PRISMA guidelines, we identified studies by searching 3 online databases (Embase, Medline, PsycInfo) and reference lists. Thirty-five studies were included in the label-based review, providing information for 1288 participants and 86 brain regions. Per region, 0–57% of the results indicated significant reductions in GM volume, while 0–23% indicated significant increases. The only region for which more than half of all results indicated significant reductions was the parietal lobe. However, these results were dispersed across subregions. The ALE meta-analysis, which included 6 whole-brain voxel-based morphometry studies totaling 278 participants and reporting 144 foci, showed no significant clusters of reduced GM volume. No material differences were observed when excluding experiments using reactive violence as outcome or subjects diagnosed with psychopathy. Possible explanations for these findings are phenomenological and etiological heterogeneity, and insufficient power in the label-based review and ALE meta-analysis to detect small effects. We recommend that future studies distinguish between subtypes of interpersonal violence, and investigate mediation by underlying emotional and cognitive processes.

1. Introduction

Over the last two decades, there have been numerous structural neuroimaging studies of interpersonal violence. However, the large number of different brain regions reported, variation in nomenclature and conflicting results have made interpretation difficult. Previous reviews have been non-systematic (e.g. Blair, 2010) or limited to small numbers of selected brain regions (e.g. Yang and Raine, 2009). It has also been common practice in reviews to conflate measures of violent behavior with indirect measures such as personality traits (e.g. poor impulse control, hostility) and psychiatric diagnoses (e.g. antisocial personality disorder [APD], psychopathy) (e.g. Brower and Price, 2001).

Understanding the neurobiological correlates of interpersonal violence is important for the development of: (1) interventions to prevent and reduce violence; (2) methods for screening and targeting individuals at risk for violence; (3) risk assessment tools informing involuntary admission, sentencing and release decisions; and (4) evaluation in criminal cases concerning the degree of a particular defendant's culpability and risk of future violence.

Therefore, we present a systematic label-based review (Radua and Mataix-Cols, 2012) of neuroimaging studies investigating the quantitative association between regional grey matter (GM) volume and interpersonal violence. We also performed an anatomical likelihood estimation (ALE) meta-analysis of voxel-based morphometry (VBM) studies examining volumetric reductions in regional GM.

2. Methods

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

2.1. Search strategy

We searched for studies indexed in the online databases Embase, Medline and PsycInfo from January 1990 to December 2014. Keywords were inclusive for violent behavior ("violen*", "aggressi*", "prison*", "crim*", "offen*"), structural neuroimaging techniques ("neuroimaging", "brain imaging", "computed tomography", "CT", "magnetic resonance imaging", "MRI", "diffusion tensor imaging", "DTI") and – to make the search more focused – brain regions that have usually

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received the most attention in neuroimaging studies of violent behavior (specifically “amygdala”, “prefrontal cortex”, “temporal cortex”). Additional studies were found by manually scanning the references of included studies and a number of recent review articles (e.g. Bufkin and Lutrell, 2005; Dolan, 2010; Fabian, 2010; Hoptman and Antonius, 2011; Patrick, 2008). Finally, we searched citations to included studies indexed in Google Scholar Citations from January 1990 to December 2014. Our search included grey literature (e.g. dissertations, conference papers, working papers). Authors were contacted if studies were unobtainable or additional information was required.

2.2. Study selection

Studies were eligible when meeting the following criteria: (1) the study contained primary data; (2) the study was available in the English language; (3) the study was conducted in or after 1990; (4) independent samples contained 10 or more participants; (5) all participants were aged 18 or older; (6) the study used in vivo neuroimaging by means of computed tomography or structural magnetic resonance imaging (including diffusion tensor imaging [DTI]); and (7) the study measured the quantitative association between violent behavior and at least one structural parameter (e.g. volume, fractional anisotropy) using between-group, correlation or regression analysis. We defined violent behavior as the intentional use of physical force to harm another person. To be included in the label-based review, the study had to provide sufficient information to code a result for at least one discrete brain region as negative, positive or non-significant. A negative result indicated a statistically significant association between violence and a reduction in GM volume, while a positive result indicated a statistically significant association between violence and an increase in GM volume. For ALE meta-analysis, we considered studies that conducted whole brain voxel-based analyses (VBAs) and reported coordinates for at least one peak voxel in either Montreal Neurological Institute or Talairach space.

We excluded: (1) samples that consisted of pedophilic offenders or participants with some form of brain lesion or malformation (e.g. cavum septum pellucidum), intellectual disability, epilepsy or a neurodegenerative disease (e.g. Huntington's disease, Alzheimer's disease); (2) analyses comparing qualitatively different types of violence (e.g. homicide versus rape); (3) psychiatric diagnoses and personality traits that are not defined by the actual display of violent behavior (e.g. psychopathy, impulsivity); and (4) instruments primarily designed to assess a person's inclination toward violent behavior (e.g. Buss-Perry Aggression Questionnaire, State-Trait Anger Expression Inventory).

2.3. Data extraction

For any combination of structural parameter and tissue class, we required a minimum of 5 experiments per: (1) brain region for label-based reviews; and (2) contrast of interest (i.e. reduction, increase) for ALE meta-analyses. Studies examining indices of white matter (WM) integrity (i.e. fractional anisotropy [$N = 5$], trace [$N = 1$], mean diffusivity [$N = 1$], radial diffusivity [$N = 1$]) with DTI, WM volume ($N = 6$) and cortical thickness ($N = 2$) contained insufficient experiments for label-based reviews and ALE meta-analyses. There was one VBM experiment of increases in GM volume of which peak-voxel coordinates were reported, precluding ALE meta-analysis. Consequently, we performed: (1) a label-based review of studies examining GM volume; and (2) an ALE meta-analysis of VBM studies examining reductions in GM volume.

The first author assessed suitability of studies for inclusion and used a standardized form to collect information from each study such as design, country, sample size, psychiatric morbidity and definition of violence. Any uncertainties were resolved by discussion with the other authors. A research assistant checked data extraction accuracy of 10 randomly selected studies; correspondence was more than 99%.

To facilitate the exploration and interpretation of results, we divided the brain into the following regions of interests (ROIs): frontal lobe; prefrontal cortex; dorsolateral prefrontal cortex (dlPFC); ventrolateral prefrontal cortex; medial prefrontal cortex; orbitofrontal cortex (OFC); anterior cingulate cortex (aCC); posterior frontal cortex; temporal lobe, lateral temporal lobe; medial temporal lobe; amygdala, hippocampus; polar temporal lobe; parietal lobe; postcentral gyrus; superior parietal lobule; inferior parietal lobule; occipital lobe; lateral occipital lobe; medial occipital lobe; cingulate cortex; posterior cingulate cortex; fusiform gyrus; temporal fusiform gyrus; occipital fusiform gyrus; striatum; and other subcortical structures (e.g. hypothalamus, cerebellum). Additional information on data extraction can be found in the online supplement.

2.4. Data analysis

2.4.1. Label-based review

Weighting by sample size, we calculated the percentages of negative, positive and non-significant results reported for each brain region. Statistical significance was determined with: (1) an α level of 0.05 (two-tailed) for results of ROI analyses; and (2) the thresholding criteria applied by the study authors for results of VBM analyses. We rejected the null hypothesis if more than 50% of the results were all either negative or positive.

2.4.2. ALE meta-analysis

ALE meta-analysis was carried out in GingerALE 2.3.6 (brainmap.org/ale). We used the non-additive algorithm (Turkeltaub et al., 2012) to minimize within-experiment effects. Inference was made at cluster-level ($p < 0.05$, 1000 permutations) with an uncorrected voxel-wise p-value of 0.005. Cluster-level inference has been shown to provide a better balance between sensitivity and specificity compared with other methods to correct for multiple comparisons currently available in GingerALE (Eickhoff et al., 2012). The α levels are in line with those used in previous ALE meta-analyses (e.g. Barron et al., 2013; Fusar-Poli et al., 2013).

2.4.3. Subgroup analyses

It has been theorized that the neurobiological correlates of violent behavior differ between reactive *vs* proactive (Rosell and Siever, 2015) and adolescence-limited *vs* life course-persistent (Moffitt and Caspi, 2001) subtypes. While we planned subgroup analyses of these subtypes for both the label-based review and ALE meta-analysis, only sufficient experiments were available to add a subgroup analysis of reactive violence to the label-based review.

2.4.4. Sensitivity analyses

To determine the robustness of the findings, we repeated both the label-based review and ALE meta-analysis after separately excluding experiments with: (1) reactive violence as outcome; and (2) samples that consisted of subjects diagnosed with psychopathy (Anderson and Kiehl, 2014).

3. Results

Fig. S1 shows a flow diagram of the search process.

3.1. Label-based review

There were 35 studies that met inclusion criteria for the label-based review. These studies contained a total of 1288 participants with a mean age of 33 years (range = 20 – 48 years). Most participants were male ($n = 1066$, 83%) and nearly half ($n = 575$, 45%) were diagnosed with one or more of the following (classes of) psychiatric disorders: axis I disorder ($n = 390$; 30%); personality disorder ($n = 276$; 21%); schizophrenia or schizoaffective disorder ($n = 244$; 19%); APD ($n =$

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