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Magnitude and variability of structural brain abnormalities in neuropsychiatric disease: protocol for a network meta-analysis of MRI studies

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31 **ABSTRACT**

32

33 **Introduction**

34 Structural magnetic resonance imaging (MRI) is the most frequently used method to

35 investigate brain volume alterations in neuropsychiatric disease. Previous meta-

36 analyses have typically focused on a single diagnosis, thereby precluding

37 transdiagnostic comparisons.

38

39 **Methods and analysis**

40 We will include all structural MRI studies of adults that report brain volumes for

41 participants from at least two of the following diagnostic groups: healthy controls,

42 schizophrenia, schizoaffective disorder, delusional disorder, psychotic depression,

43 clinical high risk for psychosis, schizotypal personality disorder, psychosis unspecified,

44 bipolar disorder, autism spectrum disorder, major depressive disorder, attention deficit

45 hyperactivity disorder, obsessive compulsive disorder, posttraumatic stress disorder,

46 emotionally unstable personality disorder, 22q11 deletion syndrome, generalised

47 anxiety disorder, social anxiety disorder, panic disorder, mixed anxiety and

48 depression. Network meta-analysis will be used to synthesise eligible studies. The

49 primary analysis will examine standardised mean difference in average volume, a

50 secondary analysis will examine differences in variability of volumes.

51

52 **Discussion**

53 This network meta-analysis will provide a transdiagnostic integration of structural

54 neuroimaging studies, providing researchers with a valuable summary of a large

55 literature.

56

57 **PROSPERO Registration number:** 221143

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59

BACKGROUND

A wide range of neuropsychiatric disorders have been associated with alterations in regional brain volumes.[1–3] Understanding whether regional patterns of structural abnormalities differ between disorders as opposed to representing a more general transdiagnostic disease process has major relevance for understanding the pathophysiology of neuropsychiatric disease.

In addition to studying differences in the mean size of regional brain volumes, recent studies have highlighted that the variability of regional volume size also differs between healthy controls and individuals with psychiatric disorders.[2,3] In some disorders, relatively homogenous volumetric changes to specific brain regions are observed, whereas other regions display more heterogenous differences, suggesting that structural alterations may only be present within certain subgroups of the diagnostic category.

Meta-analysis has frequently been used in attempts to synthesise findings from the large number of studies of brain volumes. These analyses, however, typically only examine a single disorder.[2,3] Network meta-analysis is an approach that is generally used for the comparison of efficacy across multiple health interventions, but can also be used to allow for the coherent synthesis of structural imaging studies across multiple disorders. Previous transdiagnostic meta-analyses have occasionally been reported. However, these meta-analyses either studied a restricted range of diagnoses;[4] or used an activation likelihood estimate approach, which does not allow for quantification of effect sizes and so preclude determination of whether one disorder displays a regional volumetric alteration greater in magnitude than another.[1]

In the current protocol we describe a network meta-analysis of structural MRI studies across a wide range of neuropsychiatric disorders. The primary objective of the study is to quantify patterns of similarity and differences between disorders in terms of regional brain volumes. The secondary objective is to examine how patterns of variability of brain volumes differ across neuropsychiatric diagnoses.

METHODS AND ANALYSIS

Types of studies

All relevant published observational studies that use MRI to compare brain volumes in one neuropsychiatric disorder to another, or to controls will be identified by searching the relevant international scientific literature.

Types of Participants

The eligible population consists of individuals age 18 and over, of both sexes, with established diagnoses of any of the following disorders: schizophrenia, schizoaffective disorder, delusional disorder, psychotic depression, clinical high risk for psychosis, schizotypal personality disorder, psychosis unspecified, bipolar disorder, autism spectrum disorder, major depressive disorder, attention deficit hyperactivity disorder, obsessive compulsive disorder, posttraumatic stress disorder, emotionally unstable personality disorder, 22q11 deletion syndrome, generalised anxiety disorder, social anxiety disorder, panic disorder, mixed anxiety and depression. In addition, data from control groups will be extracted. These diagnoses encompass the vast majority of neuropsychiatric disorders in terms of lifetime prevalence, with the exception of substance use disorders.[5] We have chosen not to include substance use disorders due to the difficulties in disambiguating the brain changes associated with the pathophysiology of addiction, and those that result from the direct effects of substance use.

Diagnoses should have been made using standardised diagnostic criteria such as the Research Diagnostic Criteria, Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), DSM-III-R, DSM-IV, DSM-5, International Classification of Disease, 10th Revision (ICD-10), ICD-11 or the comprehensive assessment of At-Risk Mental States.[6] Study arms explicitly examining participants with comorbid psychiatric or physical health disorders will not be included. Uncertainty regarding study eligibility will be decided by discussion between authors.

Outcome Measures

For each study we aim to collect the mean and standard deviation of volumetric (in mm3 or cm3) or thickness (mm or cm) measurements for global and/or regional brain

127   structures. Brain volumes examined will include: whole brain, whole brain white

128   matter, whole brain gray matter, whole brain cerebrospinal fluid, amygdala, anterior

129   cingulate cortex, accumbens, caudate, cerebellum, corpus callosum, frontal lobe,

130   hippocampus, insula, lateral ventricle, pallidum, parahippocampal gyrus, parietal lobe,

131   putamen, temporal lobe, thalamus, and third ventricle. If reported separately, values

132   will be extracted for both left and right hemispheres.

133

134   If only subregions of the above regions are reported (e.g. frontal pole and medial

135   frontal cortex are reported, but no overall value for frontal lobe is reported), then all

136   subregions for the region in question will be combined. For volume measurements the

137   overall mean volume measure will be obtained by summing the subregion volumes,

138   with standard deviations being calculated according to standard propagation of

139   uncertainty formula with the between region correlation assumed to be 0.7. For

140   thickness measurements overall mean volume measure will be obtained by averaging

141   the subregion thickness values, with standard deviations being calculated according

142   to standard propagation of uncertainty formula, with the between region correlation

143   assumed to be 0.7, and subregions weighted according to their estimated volume as

144   reported within the Desikan-Killany atlas [7].

145

146   If both normalised and non-normalised volumes are reported, non-normalised

147   volumes are preferred. If gray and white matter values are reported separately for a

148   region, gray matter values are preferred. If both volume and thickness measurements

149   (in mm or cm) are reported, volume measurements are preferred.

150

151   **Search Strategy**

152   The search strategy will include terms related to the study population, study type, and

153   main outcome. This search will extract studies from the following databases: Embase

154   (Ovid interface), MEDLINE (Ovid interface) and PsycINFO (Ovid interface). Hand-

155   searching will also be performed to supplement electronic database searches, this will

156   involve reviewing the reference lists of studies meeting our eligibility criteria.

157

158   *Search term:*

159   (("magnetic resonance imaging" or MRI) and volume and (schizophren* or psychosis

160   or schizoaffective or delusional or bipolar or depression or depressive or affective or

161 autism or ASD or ADHD or "attention deficit" or anxiety or OCD or "obsessive
162 compulsive" or PTSD or posttraumatic or 22q or velocardiofacial or "emotionally
163 unstable" or "borderline personality")).ab,kw,ti.
164

165 **Data extraction**
166 Extracted information will be as follows: number of participants in each group, mean
167 age, gender (% male), ethnicity (% black, white, other), psychiatric diagnosis including
168 any comorbidities, age at illness onset, illness duration, psychotropic usage, method
169 of measurement (volume vs thickness, automated vs manual), magnetic field
170 strength, units of measurement, mean ± standard deviation (SD) of regions stated
171 above.
172

173 Seven researchers will select the studies and extract the relevant information (XG, LV,
174 TAH, CC, RM, GW) into a shared google sheet. If there is evidence of overlapping
175 samples between studies, the study with the larger sample size will be used.
176

177 **Data Synthesis**
178 A qualitative synthesis of the collected data will also be presented. This will include
179 summary tables showing the characteristics of the study population - demographics,
180 diagnosis, age at illness onset, illness duration, medication use and duration of
181 pharmacological treatment, and a PRISMA flowchart.
182

183 **Pairwise meta-analyses**
184 The principal summary measure will be the standardised mean difference (Hedges' g)
185 between diagnostic groups for the volumes of different brain regions.[8]
186

187 The secondary summary measure will be the coefficient of variation ratio (CVR). This
188 is a measure of how variability differs between two groups while controlling for mean,
189 and has been used in pervious meta-analyses of brain structure to identify if there is
190 evidence of subgroup phenomena within psychiatric disorders.[2,3,9]
191

192 We will perform direct meta-analyses for all pairs with >/=3 studies to obtain mean
193 brain volume differences with their accompanying 95% confidence intervals using a
194 random effects model. Analyses will be carried out in the statistical programming

195   language R (version 3.5.1) using 'metafor' (version 2.1-0).[10] Visual inspection of the

196   forest plots will be used to investigate the degree of statistical heterogeneity, alongside

197   monitoring of τ (the estimated standard deviation of random effects) and the I2

198   statistic. An I2 of less than 25% will be deemed to correspond to low heterogeneity,

199   25-75% medium heterogeneity, and greater than 75% high heterogeneity. To help

200   visualize and assess the extent of heterogeneity we will also include prediction

201   intervals in all forest-plots.

202

203   Small study effects and publication bias will be assessed for each pairwise comparison

204   by visual inspection of the contour-enhanced funnel plot and by performing Egger's

205   test of the intercept for meta-analyses comprising at least 10 studies.[11]

206

207   **Assessment of the transitivity assumption**

208   In an attempt to ensure transitivity in the network, we will exclude studies examining

209   paediatric patients, and exclude studies in which physical and psychiatric

210   comorbidities are specifically studied.

211

212   Potential effect modifiers include age, gender, and ethnicity. As such, we will examine

213   if age, gender (% male) and ethnicity (% white) of participants is similarly distributed

214   across the different diagnoses and health control populations.

215

216   **Network Meta-analyses**

217   If there is sufficient similarity between studies in terms of age, gender and ethnicity,

218   we will conduct a random-effects network meta-analysis to synthesise our data.

219   Network plots will be generated using the 'netgraph' function from the package

220   'netmeta',[12] with each node representing a specific disorder, the size of the node being

221   proportional to the number of studies used, and the thickness of the lines (edges)

222   between nodes being proportional to the number of pairwise comparisons.

223

224   We will use a frequentist approach to network meta-analysis using 'netmeta' in R

225   (version 1.0-1). In order to allow for comparison across different scanners and

226   measurement approaches we will express volume differences between disorders as

227   a standardised mean difference (Hedge's g).

228

229 We will produce forest plots using 'ggplot2' (version 2.2.1), where the control group

230 will be used as the reference. League tables will be created to display the relative

231 degree of volume alteration for the various diagnostic groups using the 'netleague'

232 function.

233

234 For each brain region, we will use the P-scores to rank diagnostic groups based on

235 the corresponding degree of volume alteration. This will be done using the 'netrank'

236 function. This method will allow us to rank the diagnostic groups on a continuous 0 to

237 1 scale for each outcome of interest: a higher P-score indicates greater degree of

238 volume alteration. To summarise results across brain regions and disorders in a single

239 diagram we will produce a 'Kilim plot'.[13]

240

241 **Assessments of heterogeneity and inconsistency**

242 Heterogeneity of each network will be assessed by monitoring of τ and by plotting the

243 prediction intervals for all comparisons versus placebo. Consistency of each network

244 (i.e. the agreement between direct and indirect evidence) will be evaluated using a

245 global method (Q statistic) as well as a local method (back-calculation method using

246 the 'netsplit' function).[14]

247

248 **Sensitivity Analyses**

249 The ENIGMA consortium has published several large scale syntheses of

250 neuroimaging data.[15,16] It is not straightforward to determine the overlap between

251 these studies and previously published work, as a result a sensitivity analysis will be

252 ran both including and excluding ENIGMA studies.

253

254 **Meta-regression analyses**

255 In addition to neuropsychiatric disorders, multiple other genetic and environmental

256 factors also influence brain volumes. These include ageing and the use of

257 psychotropic medications. We will therefore perform a meta-regression analysis to

258 examine the relationship between study-level means of participant characteristics

259 (gender, age, ethnicity (% white), illness duration, medication use) and differences in

260 brain volumes, for each diagnosis vs. a control population. Meta-regressions will be

261   performed using the 'metafor' function in R statistical software (version 3.5.3) and plots

262   will be generated using 'ggplot2'. We will only perform this analysis for diagnoses

263   compared with controls in at least five studies.

264

265   **Risk of Bias**

266   Two independent reviewers will assess the quality of each study using a modified

267   version of the Newcastle-Ottawa Scale for case control studies in which the exposure

268   category is not considered due to its lack of relevance for imaging studies. This is the

269   most appropriate scale given that observational studies are expected to predominate.

270   Each study can receive a score from zero (low quality, high risk of bias) to six stars

271   (high quality, low risk of bias). A threshold of >/= 4 stars will be used to designate a

272   high-quality study.

273

274   The 'Confidence in Network Meta-Analysis' (CINeMA) application will be employed to

275   evaluate the credibility of findings from network meta-analysis.[14,17] As part of the

276   CINeMA evaluation process, a risk of bias assessment is required for each study with

277   each study categorised as at low, unclear, or high risk of bias, we will use the same

278   threshold of >/= 4 stars to classify studies as being at low or high risk of bias.

279

280   **Discussion**

281   Structural brain abnormalities in neuropsychiatric disease have been studied in

282   increasing depth over the past half century, with the number of studies increasing

283   dramatically following the advent of MRI. While meta-analyses of individual disorders

284   aid in the synthesis of this vast body of research, understanding how findings

285   regarding one disorder relate to another remains a major challenge. In recent years

286   studies have undertaken transdiagnostic attempts, but these involve smaller numbers

287   of participants than a meta-analytic approach allows for or do not encompass as broad

288   a range of disorders. This network meta-analysis provides a powerful approach to

289   deriving a coherent understanding of brain abnormalities across neuropsychiatric

290   disorders.

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