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1 Identification of neurobehavioural symptom groups based on 2 shared brain mechanisms

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102 **Abstract:**

103 **Most psychopathological disorders develop in adolescence. The biological**
104 **basis for this development is poorly understood. To enhance diagnostic**
105 **characterisation, and develop improved targeted interventions, it is critical to**
106 **identify behavioural symptom groups that share neural substrates. We ran**
107 **analyses to find relations between behavioral symptoms, and neuroimaging**
108 **measures of brain structure and function in adolescence. We found two**
109 **symptom groups, consisting of anxiety/depression and executive dysfunction**
110 **symptoms respectively, which correlated with distinct sets of brain regions**
111 **and inter-regional connections, measured by structural and functional**
112 **neuroimaging modalities. We found that the neural correlates of these**
113 **symptom groups were present before behavioural symptoms had developed.**
114 **These neural correlates showed case-control differences in corresponding**
115 **psychiatric disorders, depression and ADHD, in independent clinical samples.**
116 **By characterising behavioral symptom groups based on shared neural**
117 **mechanisms, our results provide a framework for developing a classification**
118 **system for psychiatric illness, which is based on quantitative**
119 **neurobehavioural measures.**

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125 Adolescence and its transition toward young adulthood is a critical period for
126 the development of psychiatric illness with half of the lifetime psychopathological
127 burden emerging by the mid-teens, and 75% by the mid-20s¹. It coincides with major
128 structural changes in grey and white matter² that are particularly pronounced in the
129 limbic system and the prefrontal cortex³. Cognitive and (other) behavioural
130 maturation reflects this brain-wide developmental process⁴. As psychopathological
131 symptoms during adolescent brain re-organization are often unspecific, and in many
132 cases reversible, it has been difficult to unambiguously identify early markers for
133 sustained mental illness. Thus, most patients present during adulthood, often at a
134 point when severe psychopathology has developed, which gravely impairs their daily
135 functioning. Presentation at this advanced stage increases individual suffering and
136 renders therapeutic interventions more difficult.

137 Currently, both adolescent and adult psychiatric diagnoses are made on the
138 basis of combinations of behavioural symptoms that - whilst reflecting the
139 psychopathological experience of generations of clinicians and patients - are not
140 necessarily related to homogeneous pathophysiological or etiological processes.
141 This results in biological heterogeneity within diagnostic entities⁵, high rates of
142 comorbidity between diagnoses^{6,7}, and ill-defined targets for drug development. This
143 is particularly relevant in adolescence, where there is evidence to suggest that
144 psychiatric illness is more dimensional and less categorical than adult
145 psychopathology. Neuroimaging methods offer the opportunity to identify the
146 biological mechanisms underpinning mental illness, without recourse to these
147 categorisations^{8,9}.

148 One of the challenges in breaking up diagnostic borders in favour of more
149 homogenous clusters of symptoms sharing common neural mechanisms, is that

150 biological and behavioral data need to be combined in a meaningful way. A suitable
151 method for this purpose is canonical correlation analysis (CCA), which is formulated
152 to maximize the correlation between variables in two views of a dataset. This
153 technique has previously been used to link complex behavioural datasets with
154 functional brain networks¹⁰. However, CCA has a number of limitations: It cannot be
155 applied to data with more features than samples, results are difficult to interpret
156 owing to a lack of localizability, and it is only possible to find relations between two
157 sets of variables. The first two of these issues can be addressed using sparse
158 canonical correlation analysis (sCCA)^{11,12}, which has been used to find modes of
159 shared variation between resting state functional connectivity MRI, and behavioral
160 measures in adolescents and young adults¹². However, this approach is still limited
161 in that it is only possible to identify relations between psychiatric symptoms and one
162 kind of biological measure at a time. We further enhanced sCCA by formulating a
163 constrained form of multiple canonical correlation analysis, which maximizes the
164 correlation between psychiatric symptoms, and several different neuroimaging
165 modalities simultaneously¹³, before combining them in a linear regression model; we
166 term this approach sparse multiple canonical correlation analysis regression
167 (msCCA-regression).

168 We investigated whether symptoms contributing to DSMV/ICD10 diagnoses
169 can be reconfigured to identify 'neurobehavioral' symptom groups that best represent
170 specific underlying dysfunctional brain networks in adolescence. Here, we used a
171 data driven approach applied to a large general population neuroimaging sample to
172 investigate direct relations between neuroimaging measures of brain structure and
173 function, yet without immediate recourse to diagnostic psychiatric categories.
174 Following this, we sought to determine whether the regions we found to be related to

175 psychiatric symptoms in adolescence were associated with fully-blown clinical
176 psychopathology in several independent clinical samples. Overall, this multi-step
177 approach enabled us to identify brain correlates of psychopathology in adolescence,
178 probe their predictive value in the critical period between age 14 and age 19, and
179 characterize these brain correlates against the development of full-blown
180 psychopathology.

181

182

183 **Results**

184 We used msCCA-regression (please see the methods section under the sub-
185 heading: Multiple Sparse Canonical Correlation Analysis Regression) to link
186 participant responses to the Development and Well Being Assessment (DAWBA), a
187 structured interview for psychiatric DSMV/ICD-10 diagnoses¹⁴ (Supplementary Table
188 1), with voxel-based morphometry (VBM)¹⁵ measures of grey matter volume,
189 fractional anisotropy (FA) along major white matter tracts using tract-based spatial
190 statistics (TBSS)¹⁶, and functional connectivity between different brain regions,
191 mapped from resting state (rs-fMRI) scans¹⁷. T₁ and DTI data were pre-processed
192 using voxel-wise VBM¹⁸ and TBSS¹⁹ methods respectively, as these procedures
193 have been extensively studied and applied to real data. We mapped inter-regional
194 rs-fcMRI connections across the brain using nodal maps defined by Miller et al¹⁷,
195 reasons for our pre-processing and analysis choices are detailed in the methods
196 section of the paper under the sub-heading: Different Neuroimaging Pre-processing
197 Strategies. We investigated ninety DAWBA items (symptoms) related to a broad
198 range of psychiatric disorders, including affective and anxiety symptoms, attention
199 deficit/hyperactivity and conduct symptoms, as well as substance use, eating

200 disorders, and symptoms of psychosis (Supplementary Table 1)¹⁴. This analysis was
201 carried out on the general population IMAGEN sample, on participants of age 19.
202 Following an in-depth QC (see methods under the sub-heading: IMAGEN analysis),
203 data for n = 666 participants was available at age 19.

204 To avoid overestimating the variance shared between psychiatric symptoms,
205 and the neuroimaging modalities analysed (overfitting), we used a train/test analysis
206 design, which allows us to estimate effect sizes in an unbiased way. Using a test set
207 also allowed us to carry out further characterization of the data, without running into
208 circularity problems. We carried out model selection in a training dataset of 70% of
209 the data (n=467), and model validation in the testing dataset of the remaining 30%
210 (n=199). To enhance stability we resampled the data and retained only variables that
211 contributed to the model in 90% of resamples (see methods under the sub-heading:
212 Stability Selection, and Supplementary Figure 1)²¹. Demographic information on the
213 full sample, training and testing sets is given in Supplementary Figure 2. The
214 msCCA-regression procedure we used in this investigation is designed to maximise
215 associations between variable-sets. For this reason, all msCCA-regression
216 significance values reported in the text are one-sided.

217
218 Using msCCA-regression, we found a significant relation between a subset of six
219 DAWBA symptoms (see Figure 1), and VBM, TBSS and rs-fMRI measures
220 ($r=0.59(465)$, $p<0.001$). The behavioural correlates derived from DAWBA covered
221 symptoms linked to feelings of depression, anxiety and somatic problems, as well as
222 temper and attentional problems (Figure 1). The model was also significant when
223 applied to the test dataset ($r=0.23(197)$, $p<0.001$, 95% CIs=0.13, ∞) (Figure 1),
224 explaining 5.30% of the variance between psychiatric symptoms and the brain. Brain

225 correlates derived from VBM, TBSS and rs-fcMRI measures were associated with
226 this anxiety/depression symptom group with correlation values of: $r=0.16(197)$,
227 $p=0.017$, 95% CIs= $0.040, \infty$; $r =0.14(197)$, $p=0.040$, 95% CIs= $0.037, \infty$ and
228 $r=0.15(197)$, $p=0.029$, 95% CIs= $0.041, \infty$ respectively (with all p-values FWE-
229 corrected for multiple comparisons, see methods under the sub-heading: Analysis
230 Design, and Supplementary Figure 3).

231 VBM, TBSS and rs-fcMRI modalities all showed an individually significant
232 relation to psychopathology. We carried out further localization analyses in each
233 modality to identify brain regions that showed an individually significant relation to
234 psychopathology (see methods under the sub-heading: Additional Analyses to
235 Localise Effects). In this localization analysis, we identified one gray matter cluster in
236 the right inferior temporal gyrus ($r=0.16(197)$, $p=0.032$ FWE corrected, 95%
237 CIs= $0.041, \infty$), and a single cluster of decreased fractional anisotropy in the genu of
238 the corpus callosum ($r = 0.16(197)$, $p=0.031$ FWE corrected, 95% CIs= $0.041, \infty$).
239 Both of these brain regions have been among those exhibiting the largest differences
240 between healthy controls and patients with depression, in recent large, well-powered
241 meta-analyses^{22,23}. Further, we found an increase in functional connectivity between
242 the default mode network, and the cerebellum ($r=0.15(197)$, $p=0.041$ FWE corrected,
243 95% CIs= $0.037, \infty$); the default mode network has been implicated in several
244 different psychiatric disorders, but depression in particular, with recent research
245 showing that connectivity between the cerebellum and the default mode network is
246 altered in patients with depression²⁴. Information on the full set of regions found to be
247 associated with psychiatric symptoms can be found in Supplementary Tables 2 and
248 3 and Supplementary Figures 4 and 5.

249 We then removed the effects of the first canonical relation and investigated
250 the presence of a second dimension of shared variance between symptoms and the
251 brain (see methods under the sub-heading: Finding Multiple Modes of
252 Variation). Here, we identified another behavioral correlate consisting of five items
253 from the DAWBA, including: problems with attention, fidgeting, rapidly changing
254 moods and (lack of) conscientiousness that was significantly associated with the
255 neuroimaging modalities ($r=0.46(465)$, $p=0.004$). The test sample correlation is
256 significant at ($r=0.19(197)$, $p=0.002$, 95% CIs= $0.087, \infty$), explaining 3.61% of the
257 variance between psychiatric symptoms and the brain. Brain correlates derived from
258 VBM, TBSS and rs-fcMRI measures were associated with the executive dysfunction
259 symptom group with correlation values of $r=0.19(197)$, $p=0.012$, 95% CIs= $0.079, \infty$;
260 $r=0.070(197)$, $p=0.21$, 95% CIs= $-0.029, \infty$ and $r=0.020(197)$, $p=0.58$, 95% CIs= $-$
261 $0.090, \infty$ respectively. These results are displayed in Figure 2.

262
263 As the VBM modality was the only modality in this second canonical relation
264 to show an individually significant relation to psychopathology, we only carried out a
265 localization analysis for VBM data in this modality; we found that executive
266 dysfunction symptoms correlated with a single grey matter cluster in the right middle
267 temporal gyrus ($r = 0.16(197)$, $p = 0.024$ FWE corrected, 95% CIs= 0.049), an area
268 that has previously been shown to be associated with ADHD symptomology²⁵.
269 Information on the full set of regions found to be associated with psychiatric
270 symptoms can be found in Supplementary Tables 4 and 5 and Supplementary
271 Figures 4 and 5. Associations between canonical anxiety/depression and executive
272 dysfunction canonical correlates are given in Supplementary Table 6. Our results
273 were robust to different rs-fcMRI atlas choices, as shown by repeated analyses using

274 a different nodal definition²⁰, which generated similar results (Supplementary Figure
275 6).

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278 **Hypothesis Driven Analysis**

279 To determine if the canonical symptom groups identified in our data-driven analysis
280 show a stronger relation to neuroimaging measures than existing means of
281 organizing psychiatric symptoms, we carried out a hypothesis driven analysis using
282 internalizing and externalizing symptoms, which are often used in adolescent
283 psychiatric diagnostics. We tested whether the canonical symptom groups identified
284 with msCCA-regression were able to explain more variance than this widely used
285 model of illness (see methods under the sub heading: Hypothesis Driven Analysis)²⁶.

286 We term these pre-defined symptom groups as DAWBA-internalising and DAWBA-
287 externalising. We found that the correlation of the DAWBA-internalising dimension of
288 psychopathology with neuroimaging measures only shows trend-level significance in
289 the test set ($r=0.12(197)$, $p=0.060$, 95% CIs= $-0.02, \infty$) and explains 1.9% of variance.

290 Similarly, DAWBA-externalising dimensions of psychiatric illness correlated with
291 neuroimaging measures at ($r=0.040(197)$, $p=0.28$, 95% CIs= $-0.095, \infty$) in the test
292 set, explaining 0.16% of the variance (Supplementary Figure 7). We then used a
293 modified version of Dunn and Clarke's $z^{27,28}$ to test directly whether the association
294 of the canonical symptom groups with the brain was significantly stronger than their
295 pre-defined analogues. While the symptom-brain correlation of the executive-
296 dysfunction symptom group was indeed significantly stronger than that of the
297 DAWBA-externalizing symptom group ($Z=1.95(196)$, $p = 0.029$), we did not find
298 evidence that the strength of the association between the anxiety/depression

299 symptom group and the brain was significantly larger than that of the DAWBA-
300 internalizing group ($Z=0.92(196)$, $p = 0.18$).

301

302 **Longitudinal Analysis**

303 We carried out the initial cross-sectional analysis relating psychiatric symptoms to
304 brain at age 19, as most psychopathological symptoms will have become manifest
305 by this age. To investigate how adolescent brain development relates to the
306 development of psychopathological symptoms, we analyzed data from the same
307 participants at age 14 years. First, we repeated the cross-sectional msCCA-
308 regression analysis using VBM and TBSS (rsfMRI data was not available at age 14).
309 We found a non-significant, trend level association between symptoms and
310 neuroimaging measures of $r = 0.42(410)$, $p = 0.11$ in the training set. We found
311 similarly non-significant results in the testing set ($r = 0.10(180)$, $p = 0.090$, 95% CIs=
312 $0.017, \infty$). The results of these analyses are displayed in Supplementary Figure 8.

313 There is previous evidence to suggest that neuroimaging measures precede the
314 development of psychiatric symptoms in adolescence²⁹. We tested whether that was
315 the case with the canonical symptom groups established in the present study by
316 extracting the TBSS and VBM regions discovered at age 19 and using them as
317 regions of interest at age 14. In order to obtain unbiased estimates of effect, we
318 looked for associations in the test sample. After a conservative quality control
319 procedure (see methods under the sub-headings: Longitudinal Analysis), $n = 182$
320 participants were available for analysis at this time-point. Our data did not show any
321 evidence of an association between anxiety/depression brain correlates and
322 anxiety/depression symptoms at 14 years $r=0.020(180)$, $p=0.40$, 95% CIs= $-0.10, \infty$.
323 However, the brain correlates taken from data at age 14, were predictive of

324 symptoms at age 19 $r=0.14(180)$, $p=0.023$, 95% CIs= $0.022, \infty$. These results are
325 shown in figure 3. The difference in correlation between brain correlates at age 14
326 years with anxiety/depression symptoms at 14 years and 19 years was also
327 significant, testing for a difference in association using a modified version of Dunn
328 and Clarke's Z ($Z=1.74(179)$, $p=0.041$)²⁸. We did not find evidence of an association
329 between brain correlates and symptoms of executive dysfunction at age 14 years
330 ($r=0.030(180)$, $p=0.41$, 95% CIs= $-0.093, \infty$). Prediction of symptoms at 19 years
331 showed a trend towards significance ($r=0.11(180)$, $p=0.065$, 95% CIs= $-0.010, \infty$).

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336 **Clinical Characterization**

337 We investigated whether the canonical correlates of psychopathology we identified in
338 a general population adolescent sample are correlated with fully developed
339 psychiatric illnesses. In these analyses, we looked for case-control differences in the
340 anxiety/depression and executive dysfunction canonical correlates, across four
341 common psychiatric illnesses in several independent clinical samples. We carried out
342 these analyses using VBM data alone, as this was the only data modality that
343 showed an individually significant association with both symptom groups. Clinical
344 and demographic information associated with the different clinical samples is
345 displayed in Supplementary Figure 9 and Supplementary tables 7-9. Extensive
346 information on quality control and data exclusion criteria for these clinical samples is
347 given in the methods section of this paper following the sub-heading: Clinical

348 Analyses. In assessing this data, we were looking for a directional effect, we
349 therefore report significance levels resulting from one-tailed tests in this section of
350 the paper.

351 When analyzing the data for case-control differences in grey matter correlates
352 of anxiety/depression symptoms, we found significant reductions in regional grey
353 matter volume in independent samples of patients with Depression (t-
354 statistic=4.61(612), $p < 0.001$, Cohen's $D = 0.39$, 95% CIs=0.25, ∞), Schizophrenia (t-
355 statistic=2.54(445), $p = 0.002$, Cohen's $D = 0.25$, 95% CIs = 0.087, ∞) and in ADHD (t-
356 statistic=1.84(203), $p = 0.034$, Cohen's $D = 0.26$, 95% CIs=0.030, ∞). In the executive
357 dysfunction grey matter correlates, we found significant differences between patients
358 and healthy controls in ADHD (t-statistic=2.19(203), $p = 0.014$, Cohen's $D = 0.32$, 95%
359 CIs=0.070, ∞), Schizophrenia (t-statistic=2.84(445), $p = 0.0026$, Cohen's $D = 0.28$, 95%
360 CIs=0.11, ∞) and Depression (t-statistic=1.65(612), $p = 0.050$, Cohen's $D = 0.14$, 95%
361 CIs=0.001, ∞). We did not find significant effects of bipolar disorder along either of
362 these dimensions (t-statistic=-0.23(473), $p = 0.59$, Cohen's $D = -0.02$, 95% CIs=-0.17,
363 ∞) and (t-statistic=-1.33(473), $p = 0.90$, Cohen's $D = -0.12$, 95% CIs=-0.27, ∞)
364 respectively (Figure 4). In these case-control analyses, the data distribution was
365 assumed to be normal but this was not formally tested. To test whether the observed
366 reduction in grey matter was specific to the brain correlates identified, as opposed to
367 being a proxy for a generalized, brain-wide reduction in grey matter, we repeated the
368 clinical comparisons using total grey matter as a covariate of no interest in addition
369 to total intracranial volume (Supplementary Figure 10). ADHD and Depression
370 results were unaffected by this change in pre-processing. In contrast, the
371 Schizophrenia results were no longer significant.

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375 **Discussion**

376 We ran analyses to establish direct relations between psychiatric symptoms and
377 neuroimaging measures of brain structure and function, without immediate reference
378 to pre-defined psychiatric categories. This kind of dimensional, data-driven,
379 approach is particularly relevant in adolescence where there is a good deal of
380 evidence suggesting that psychopathology is less differentiated than in adulthood
381 and therefore doesn't fit into the traditional categorical conception of psychiatric
382 disorder^{30,31}. We find two largely non-overlapping sets of brain regions that correlate
383 with different sets of psychiatric symptoms. The first symptom dimension
384 predominantly encompassed anxiety/depression symptoms whilst the second
385 dimension mainly consisted of executive dysfunction symptoms.

386 The anxiety/depression canonical symptom correlate was significantly associated
387 with T₁, rs-fcMRI and DTI data modalities. Participants scoring highly on this
388 psychiatric scale showed decreased grey matter volume in the middle temporal
389 gyrus, reduced fractional anisotropy in the genu of the corpus callosum, and
390 increased functional connectivity between the default mode network and the
391 cerebellum. A recent meta-analysis has demonstrated an association of depression
392 with the right inferior temporal gyrus²², a region exhibiting close connections with the
393 limbic system, consistent with the theory that depression results from dysfunctional
394 cortico-limbic circuits³². The genu of the corpus callosum is a commissural white
395 matter pathway that links left and right prefrontal brain regions³³. Changes in the
396 structure of the corpus callosum are known to result in altered inter-hemispheric
397 connectivity and impaired emotional control³⁴. The genu of the corpus callosum has
398 been shown to be the white matter region with the largest difference in FA between

399 controls and patients with major depression³⁵. The default-mode network is a set of
400 brain regions that reliably exhibit a decrease in activity when the brain is engaged in
401 non-self-directed tasks; this network is thought to be primarily responsible for self-
402 inspection and internal monitoring^{36,37}, which are processes overactive in
403 depression³⁸. Increased connectivity between the default-mode network and the
404 cerebellum has been previously reported in drug-naive depressive patients²⁴,
405 consistent with its recently discovered involvement in complex cognitive and
406 emotional processes³⁹.

407 We found that the executive dysfunction psychiatric symptom group was significantly
408 correlated with neuroimaging measures derived from T₁ data. Here, decreased grey
409 matter was localised to the Right Middle Temporal Gyrus, previously linked to
410 ADHD²⁵. These results are more difficult to interpret as the function of this brain area
411 is not well studied. As with the rest of the temporal lobe, this brain area is thought to
412 be responsible for generating meaning from sensory inputs¹⁹. Further, the temporal
413 lobe functions in close relation with the hippocampus in the formation of memories¹⁹.
414 Therefore, atrophied grey matter in this brain area may help explain the learning
415 deficits often observed with ADHD-like symptoms.

416 The identification of brain systems from a population-based cohort that is not
417 suffering from any other psychiatric illness has major advantages: By identifying sub-
418 clinical correlates of psychiatric illness, prior to the full manifestation of disorder, it is
419 possible to avoid the potential impact of effects indirectly related to illness, such as
420 substance use and medication effects. For example, 17% percent of the
421 schizophrenia, and 21% percent of the Bipolar samples but none of the healthy
422 controls studied here have a history of alcohol abuse, which has been linked to
423 widespread decreases in grey matter⁴⁰. In addition, various psychiatric medicines,

424 including lithium, which is often prescribed to Bipolar patients, have also been linked
425 to alterations in grey matter volume⁴¹, it is possible that lithium-induced increases in
426 grey matter volume may have contributed to the observed absence of significant
427 findings in Bipolar patients in this study.

428 We compared the efficacy of the data-driven msCCA-regression method with
429 pre-defined psychiatric scales of internalising and externalising symptoms. We found
430 that the data driven approach identified relations between symptoms and the brain
431 that were significantly stronger than a similar approach using standard internalising
432 and externalising psychiatric symptom scales, defined without reference to any
433 underlying biology. The fact that the canonical symptom groups show a stronger
434 correlation with neuroimaging measures than pre-defined scales is important as it
435 shows that data driven methods may offer the potential to refine existing psychiatric
436 categorisations⁶.

437 It is notable that grey matter correlates of psychopathology are already
438 present at age 14 years, preceding the development of symptoms that only become
439 manifest 5 years later, at 19 years. We also found that the brain correlates
440 identified in the adolescent general population replicate in independent clinical
441 samples of corresponding psychiatric disorders, namely depression and ADHD. In
442 addition to validating our primary results gained from population cohorts, these
443 results raise the prospect of using neuroimaging measures, discovered in preclinical
444 samples, as predictors of future psychopathology, thus enabling the development of
445 targeted interventions in a young age group, where such measures are most
446 effective in reducing the burden of mental illness⁴².

447 It is important to note that the results of the msCCA-regression analysis
448 applied here, depend on the distribution of prevalence of psychopathological

449 symptoms in each sample investigated. Thus, while a general population sample
450 may yield an index of the normative variance in psychiatric symptoms from
451 a broader range of different psychiatric disorders and their neural correlates, a
452 patient sample might yield a narrower biological stratification within distinct clinical
453 psychiatric categories, e.g. different biotypes of depression⁵, or symptoms
454 of psychosis.

455 By basing symptom groups upon brain correlates, and by demonstrating
456 specific associations of these correlates with clinical psychopathology, we have
457 characterized stratification markers based on shared neural substrates. By
458 discovering that these brain correlates identified in young adults are already
459 established during adolescence, we have characterized biological risk markers prior
460 to the manifestation of symptoms. Our work thus shows how major obstacles can be
461 overcome in developing a taxonomy for psychiatric illness based on quantifiable
462 neurobehavioral phenotypes.

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480 **Methods**

481 **Ethics Statement**

482 **IMAGEN**

483 Each site sought and received approval from the relevant local research ethics
484 committee. Written consent was obtained from each participant and a parent or
485 guardian.

486 **Munich-Depression**

487 The studies were approved by the respective local ethics committees: The ethical
488 committee of the Ludwig-Maximilians-Universität, Munich, Germany and the ethical
489 committee of the Bayerische Landesärztekammer, Munich, Germany. All participants
490 provided written informed consent.

491 **TOP**

492 All participants were recruited between 2003 and 2009 as part of an ongoing study of
493 psychotic disorders (Thematically Organized Psychosis study). After complete
494 description of the study, all participants gave informed consent to participate. The

495 study was approved by the Regional Committee for Medical Research Ethics and the
496 Norwegian Data Inspectorate.

497 **ADHD**

498 This study was approved by the regional ethics committee (Centrale Commissie
499 Mensgebonden Onderzoek: CMO Regio Arnhem – Nijmegen; 2008/163; ABR:
500 NL23894.091.08) and the medical ethical committee of the VU University Medical
501 Center. Informed written consent was obtained from each participant. For children
502 under 18, both parents and children gave consent.

503 **Study Protocol**

504 We developed a method, termed msCCA-regression to find multivariate relationships
505 between psychiatric symptoms, and multiple neuroimaging modalities
506 simultaneously; In this case, voxel-based morphometry (VBM)¹⁸ measures of grey
507 matter volume, fractional anisotropy (FA) derived from DTI data, and normalized
508 using tract based spatial statistics (TBSS)¹⁹, and resting state functional connectivity
509 neuroimaging measures⁴³. msCCA-regression analysis was carried out in the
510 general population IMAGEN sample, when participants were aged 19. Additional
511 analyses were then applied in order to localize associations between psychiatric
512 symptoms, and neuroimaging measures of brain structure and function. We then
513 analyzed neuroimaging and symptom data at age 14 in order to determine whether
514 this multivariate relationship already existed at this earlier time-point. Following this,
515 we assessed the clinical significance of our findings by conducting case-control
516 comparisons of the structural markers found in the IMAGEN analysis, in several
517 clinical samples. The following text gives a more detailed description of the methods
518 described here.

519 **IMAGEN Analysis**

520 IMAGEN is a large-scale neuroimaging-genetics cohort study conducted with the aim
521 of understanding the biological basis of individual variability in psychological and
522 behavioural traits, and their relation to common psychiatric disorders⁴⁴. The study
523 involves a thorough neuropsychological, behavioural, clinical and environmental
524 assessment of each participant. Participants also undergo biological
525 characterisation, with the collection of T₁ weighted MRI (sMRI), diffusion tensor
526 imaging (DTI), task-based fMRI (t-fMRI), resting-state fMRI (rs-fcMRI) and genetic
527 data. We used T₁ weighted, DTI, and rs-fcMRI data in the current investigation.

528 **Participants**

529 The analysis was carried out on participants drawn from the IMAGEN sample (see
530 for further details: Schumann et al⁴⁴. For IMAGEN, a general population sample of
531 Caucasian adolescents were recruited from eight sites across France, Ireland,
532 England and Germany. Data was collected at age 14, 16 and 19 years. After a
533 conservative quality control of MRI acquisitions and DAWBA questionnaires,
534 participants with complete data were used in the subsequent data analysis. No
535 statistical analyses were used to pre-define sample size. However, the sample size
536 used was similar to that reported in previous studies^{10,12}.

537 **DAWBA**

538 Psychiatric symptoms of the IMAGEN participants were assessed using screening
539 questions from the development and wellbeing assessment (DAWBA), a wide
540 ranging psychiatric screening questionnaire⁴⁵. Participants were asked screening
541 questions, assessing symptoms of: specific fears, social fears, stress after a very

542 frightening event, obsessions and compulsions, worrying, depression, rapidly
543 changing mood, attention and activity, troublesome behavior, drug and alcohol use,
544 concern about appearance and strange/frightening experiences; if enough of these
545 questions were answered in the affirmative, a more in-depth assessment of
546 symptoms associated with that disorder was made. DAWBA screening questions
547 have previously been used to define subthreshold clinical symptoms in neuroimaging
548 studies of subclinical psychopathology⁴⁶. The strength and difficulties questionnaire
549 (SDQ) was also used in the present investigation as this questionnaire contributes to
550 the assignment of diagnostic status in the DAWBA⁴⁵. Questions in the SDQ are
551 categorized into broad internalising and externalizing domains. The data of four of
552 the questions asked had a standard deviation of zero amongst the participants
553 asked, and were therefore not used in subsequent analyses. The full set of
554 psychiatric questions asked in the present investigation can be found in
555 Supplementary Table 1, the questionnaire items that were omitted from the analysis
556 are marked here. At the time of the analysis conducted here, DAWBA/SDQ data had
557 been collected for 1510 participants. Of these, data was incomplete for 239
558 participants, and was not used.

559

560 **T₁ Weighted MRI Acquisition**

561 Scanning took place at eight different sites across Europe, using scanners built by
562 four different manufacturers (Siemens, Philips, General Electric, Bruker). High
563 resolution, T₁ weighted images were obtained using a Magnetization Prepared Rapid
564 Acquisition Gradient Echo (MPRAGE) sequence, based on the ADNI protocol
565 (<http://www.loni.ucla.edu/ADNI/Cores/index.shtml>). Scan parameters were
566 standardized across sites to the highest degree possible (sagittal slice plane;

567 repetition time: 2.3 s; echo time 2.8 ms; flip angle 8°; 256×256×160 matrix; isotropic
568 voxel size: 1.1 mm).

569 **VBM Pre-processing**

570 At the time this investigation was conducted, T₁ data had been acquired for 1400
571 participants. All scans were visually inspected and manually reoriented. 285 scans
572 were discarded from the analysis for either movement artifacts, strong field
573 inhomogeneities, abnormal field of view, abnormally reduced cerebellum and for
574 brace artefacts. The resulting 1,115 scans were used to build the study specific
575 template. Baseline and Follow up two scans were preprocessed using both the 2008
576 version of the Voxel Based Morphometry toolbox (VBM8) running in SPM8 (v.5236).
577 Given the young adults recruited in IMAGEN, we first used VBM8 in order to avoid
578 using adult tissue probability maps (TPM) to initiate the segmentation process. The
579 VBM8 toolbox segmentation relies on an adaptive Maximum a Posterior technique
580 and TPMs used in VBM8 are for registration purposes only. Diffeomorphic
581 registration (Dartel) was then used to register the 1,115 images, and to generate the
582 study-specific population average template⁴⁷. We then resliced the data to
583 1.5x1.5x1.5mm voxel size. Smoothing was carried out using an isotropic 8 mm full
584 width at half maximum Gaussian smoothing kernel. We created a mask for the
585 sample by taking the mean across all VBM maps included in the sample. We
586 thresholded the mask at >0.4. We used a stringent mask to avoid overfitting the
587 data⁴⁸. We then extracted all voxel values within this mask, resulting in 241,544 grey
588 matter voxels.

589 **DTI Acquisition**

590 Diffusion tensor imaging acquisition sequence based on the study by Jones et
591 al⁴⁹. Diffusion tensor images were acquired using an Echo Planar imaging sequence
592 ($b=0$ and 32 directions with b -value 1300 s/mm^2 ; axial slice plane; echo time =
593 104 ms ; $128 \times 128 \times 60$ matrix; voxel size $2.4 \times 2.4 \times 2.4 \text{ mm}$), adapted to tensor
594 measurements (for example, FA, mean diffusivity (MD)) and tractography analysis.

595

596 **TBSS Pre-processing**

597 At the time this study was conducted, DTI data had been acquired for 1412
598 participants. Of these, 71 were not usable due to: signal dropouts or too much
599 rotation. Diffusion imaging data was pre-processed using software from the FSL
600 toolbox (www.fmrib.ox.ac.uk/fsl)⁵⁰. We preprocessed the remaining 1341 scans
601 using tract based spatial statistics (TBSS)¹⁹. Pre-processing was carried out in the
602 following manner: An affine registration was applied to the first B_0 image for head
603 motion and eddy current correction. Brain extraction was carried out using BET.
604 Diffusion tensor fitting was then used to obtain fractional anisotropy (FA) maps for
605 each participant. All participants' FA data was aligned into a common space using
606 the non-linear registration tool FNIRT, using a b-spline representation of the
607 registration warp field. The mean was then taken across all FA maps to create an FA
608 averaged image. This map was then 'thinned' to create a mean FA skeleton, which
609 was then thresholded at $FA > 0.2$, keeping only the major white matter tracts. Each
610 participant's aligned FA data was then projected onto the mean skeleton. We then
611 used these skeletonised maps in all subsequent analyses. The final mask used
612 contained 106,812 voxels. A further 10 scans were not used due to masking or
613 normalization issues in TBSS.

614 **Resting State fMRI Acquisition**

615 Resting state fMRI scanning of the IMAGEN participants was carried out at multiple
616 sites. The following parameters were standardized: number of volumes (164), TR =
617 2.2s, TE = 30ms, flip angle = 75, number of slices/ddas = 40/3, slice thickness = 2.4
618 mm, slice gap = 3.4 mm, voxel size = 3.4 x 3.4 x 2.4 mm³, matrix size = 64², FOV =
619 218 mm.

620 **Resting State fMRI Preprocessing**

621 At the time of this investigation, we had collected rsfMRI scans for 1067 participants.
622 Of these scans, 157 were not used, either because over 5% of scans in that
623 participant exhibited artifacts of some kind, or if over 5% of volumes showed a
624 fractional displacement of over 0.5mm. Preprocessing of resting-state data was
625 performed with routines from FMRIB's Software Library (FSL v5.0.9)⁵⁰ and Advanced
626 Normalization Tools (ANTs v1.9.2)⁵¹.

- 627 1) Motion correction was carried out, applying a rigid body registration of each
628 volume to the middle volume (FSL MCFLIRT).
- 629 2) Non-brain tissue was removed (FSL BET).
- 630 3) Spatial smoothing was applied using a 5mm FWHM Gaussian kernel.
- 631 4) Independent component analysis (FSL MELODIC) was run for each data set.
632 Artifact components were identified using an automatic classification
633 algorithm, and subsequently regressed from the data (ICA-AROMA v0.3)^{52,53}.
634 ICA-AROMA⁵² has been shown to be as effective as motion parameter
635 regression, with additional spike regression and 'scrubbing', in the removal of

636 motion related effects on functional connectivity measures derived from
637 resting state fMRI data. However, this procedure has the additional benefit
638 that it preserves more signal of interest than these methods⁵³.

639 5) The resulting cleaned data set was de-trended (up to a third degree
640 polynomial).

641 6) Co-registration to a high-resolution T₁ image (FSL FLIRT using the BBR
642 algorithm), and normalization to 2mm isotropic MNI standard space (ANTs)
643 was carried out.

644 7) We used the CompCorr procedure to further clean the data of physiological
645 noise⁵⁴. To do this: we created white matter (WM) and cerebrospinal fluid
646 (CSF) masks by taking the mean of the WM and CSF segmentations from the
647 VBM analysis, and thresholding them at 0.95, we then resliced these maps
648 into the same space as the rsfMRI data. We then extracted timecourses from
649 voxels within these regions, and took the first three principal components of
650 this signal for both WM and CSF maps. These six principal component signals
651 should represent non-neuronal signal. We then regressed this non-neuronal
652 signal from voxel timecourses across the rest of the brain.

653 8) Lastly, preprocessed and normalized resting-state data sets were resliced to
654 3mm isotropic voxels.

655

656

657 **Mapping rs-fMRI data**

658 1) We first generated 55 regional nodal timecourses using dual regression on
659 nodal regions established in the UK biobank sample¹⁷.

660 2) We mapped the correlation between nodal regions using Pearson's pairwise
661 correlation coefficient, for each participant, thus producing a connectivity
662 matrix for each participant. This connectivity matrix consists of 1,485
663 connections between nodes.

664 3) We then transformed these connectivity values using Fisher's Z-score
665 transform.

666 **Different Neuroimaging Processing Strategies**

667 A wide range of different preprocessing strategies can be applied in the analysis of
668 neuroimaging data. Approaches to analysing DTI and T1 can be categorised into two
669 broad types: voxelwise, and atlas based approaches^{18,55}. We chose to analyse this
670 data at the voxelwise level, as this allows for the highest level of spatial specificity.
671 Although it is also technically possible to analyse rs-fcMRI data across the whole
672 brain at the voxelwise level, this approach results in an enormous number of
673 features: When mapping connectivity at the voxelwise level, in a dataset made up of
674 N voxels, we are left with $(N*(N-1))/2$ connections between those voxels. In the
675 current investigation, $N = 57,053$, leading to $N*(N-1)/2 = 1.63$ billion inter-regional
676 connections. This would lead to a huge amount of redundancy in the data and
677 computational, statistical and interpretational issues. For this reason, we mapped the
678 connectivity between a pre-defined set of nodes. We used nodal definitions resulting
679 from previous work applying independent component analysis (ICA) to the UK
680 biobank sample¹⁷. We used this nodal definition as it derives from the largest extant
681 sample of neuroimaging data. In order to test whether the results we obtained were

682 robust to different nodal definitions, we also mapped inter-regional connectivity using
683 the widely used Power atlas⁵⁶ and achieved similar results (Supplementary Figure
684 6).

685 **Canonical Correlation Analysis and Sparse Canonical Correlation Analysis**

686 Canonical correlation analysis (CCA) is a very general statistical method used to
687 identify linear relationships between two or more sets of variables⁵⁷. It can be
688 thought of as a generalization of multiple linear regression. The objective of CCA is
689 to identify a relationship between two (or more) sets of variables, where there is no
690 distinction between which variables are considered dependent, and which are
691 considered independent. This method identifies weights for each variable, such that
692 the weighted sum of variables in each set is maximally correlated with the weighted
693 sum of variables from the opposite set, assuming a linear relationship.

694 Consider two matrices X_1 and X_2 , where each row denotes one of n observations,
695 and each column denotes one of p_1 or p_2 features. CCA seeks to find the weight
696 vectors w_1 and w_2 that maximise the correlation:

$$697 \quad \rho = \text{corr}(X_1 w_1, X_2 w_2).$$

698 This optimisation problem can be written as:

$$\rho = \max_{w_1, w_2} w_1^T X_1^T X_2 w_2$$

699 Subject to the constraints:

$$700 \quad w_1^T X_1^T X_1 w_1 = 1 \text{ and } w_2^T X_2^T X_2 w_2 = 1.$$

701 We assume that the columns of X_1 and X_2 have been standardised to have a mean of
702 zero and a standard deviation of one. The vectors $X_1 w_1$ and $X_2 w_2$ are referred to as
703 canonical variates.

704 Classical CCA is extremely powerful, but cannot be applied in situations where there
705 are a more features than samples (i.e., $p_1 > n$ or $p_2 > n$, which is typically the case in
706 neuroimaging studies). Interpreting and describing results from CCA can be difficult
707 because the estimated weights are not sparse. This means that some variables may
708 make negligible but non-zero contributions to the variance explained between sets.
709 Sparse canonical correlation analysis (sCCA) was developed to address these
710 issues^{11,58,59}.

711 sCCA uses an L_1 penalty on canonical weights, which forces some of them to take a
712 value of exactly zero. Furthermore, sCCA can also be applied in scenarios where
713 there are more features than samples ($p > n$). The optimization criteria for sCCA can
714 be written in the following manner:

$$\rho = \max_{w_1, w_2} w_1^T X_1^T X_2 w_2$$

715 Subject to the constraints:

716 $\|w_1\|^2 = 1$, $\|w_2\|^2 = 1$, $\|w_1\|_1 \leq c_1$ and $\|w_2\|_1 \leq c_2$

717 Here, c_1 and c_2 are assumed to fall within the bounds $1 \leq c_1 \leq \sqrt{p_1}$ and $1 \leq c_2 \leq \sqrt{p_2}$,
718 where p_1 and p_2 are the number of features in views X_1 and X_2 respectively.

719 **Multiple Sparse Canonical Correlation Analysis Regression**

720 The formulation of sparse canonical correlation analysis described in the text above
721 is designed to find relations between two views of a dataset. However, we have

722 collected data from several different neuroimaging modalities, and would like to
723 utilize information from each of them. A somewhat naive approach to finding
724 relations between psychiatric symptoms and multiple neuroimaging measures would
725 be to include all available neuroimaging modalities in one view of the canonical
726 relation, with psychiatric symptoms in the other view. However, this approach is likely
727 to be problematic as different modalities are associated with very different numbers
728 of features. For example, the functional connectivity data used in the present
729 investigation has only 0.6% of the number of features that the VBM data has. As
730 such, if these modalities were entered into the same model, the VBM data would
731 overwhelm the functional connectivity data.

732 We developed an approach designed to maximise the cross-correlation between
733 psychiatric symptoms, and multiple neuroimaging modalities simultaneously, we then
734 combined these modalities in a linear regression model. Formulations of canonical
735 correlation analysis that are able to find relations between more than two sets of data
736 are termed multiple or generalised canonical correlation procedures. A widely used
737 optimisation criteria for multiple canonical correlation analysis is to maximise the sum
738 of correlations between each of the different views of a dataset⁶⁰. Witten et al have
739 formulated a sparse version of multiple canonical correlation analysis⁵⁸; this
740 formulation is designed to maximise the sum of correlations between all views of the
741 data. However, in the present investigation, we are only interested in finding
742 correlations between neuroimaging measures, and psychiatric questionnaire
743 responses; we do not wish to optimise the correlation between different
744 neuroimaging measures.

745 As such, we seek to maximise the following relation:

$$\max_{w_1, \dots, w_n} w_1^T X_1^T \sum_{i=2}^n X_i w_i$$

746 Subject to the constraints:

747 $\|w_1\|^2 = 1, \|w_i\|^2 = 1, \|w_1\|_1 \leq c_1$ and $\|w_i\|_1 \leq c_i$

748 This method simultaneously optimizes the correlation between a weighted sum of
749 variables in the target set, X_1 , with a weighted sum of variables in the other sets. In
750 the present investigation, X_1 is a matrix of psychiatric symptoms and X_2 to X_n are
751 neuroimaging measures of brain structure and function. Using this method, we are
752 able to maximise the correlation between psychiatric symptoms, and several
753 different neuroimaging modalities within the same integrated model. A natural choice
754 for the statistic of interest, in any inference carried out using this procedure, would be
755 the sum of correlations between the symptom data, and the neuroimaging measures
756 of brain structure and function. However, a sum of correlations is of less practical
757 benefit than understanding how much total variance is shared between
758 neuroimaging measures of brain structure and function, and psychiatric symptoms.
759 Therefore, in the final step of this process, we combine canonical neuroimaging
760 variables in an ordinary linear regression model. Canonical variables are defined as:

$$C_i = X_i w_i$$

761 Canonical variables are then combined in the prediction of psychiatric symptoms
762 using ordinary linear regression:

$$C_1 = \beta_0 + C_2\beta_2 \dots + C_n\beta_n + \epsilon$$

763 We used this approach to establish relations between psychiatric symptoms (C_1),
764 and TBSS (C_2), VBM (C_3), and connectivity measures (C_4) derived from rs-fMRI data
765 and β_n are the associated weights estimated using ordinary linear regression (β_0 is
766 the constant estimated in regression).

767 msCCA-regression was carried out using in-house codes written in MATLAB. This
768 algorithm requires an initialization value. In the present study, initial weights were
769 randomly generated. Weight values associated with psychiatric symptoms were
770 always constrained to be positive to ensure interpretability.

771 This study is designed to be exploratory in nature. Nevertheless, given the very large
772 quantity of data we sought to integrate, it is likely that some simple priors will help to
773 improve the stability of our results, so long as those priors are well supported. There
774 is a great deal of evidence suggesting that psychopathology is associated with
775 decreases in both grey matter, and fractional anisotropy, across psychiatric
776 disorders^{61,62}. For this reason, we constrained the canonical weights on VBM volume
777 and FA to be negative. This will help to reduce variance in the model and will help
778 increase interpretability of our results. In contrast, there is no clear evidence that
779 psychiatric illness is associated with increases or decreases in connectivity
780 measures derived from BOLD-fMRI. Therefore, we did not add constraints to the
781 functional connectivity data.

782

783 **Stability Selection**

784 Although msCCA-regression (and sCCA) have advantages over classical CCA in
785 terms of interpretability, it can suffer from instabilities due to their utilization of an L_1
786 penalty to introduce sparsity²¹. This is particularly true when $p \gg n$, and when there
787 is a high degree of collinearity in the data. Stability selection is a widely applicable
788 feature selection procedure that can address this problem²¹. This procedure has the
789 added benefit that it makes the results less sensitive to the choice of L_1 penalty.

790 The conceptual underpinning of stability selection is very simple: if a model is
791 repeatedly resampled, features exhibiting a 'real' effect will be selected more often
792 than noise. Using stability selection, data is repeatedly split into random sub-samples
793 of size $n_t/2$ (where n_t is the total number of participants in the training dataset). In this
794 work, resampling was carried out a hundred times. msCCA was applied to each
795 resample, and those features that appear more often are deemed to be more stable.
796 Deciding which variables are stable requires a threshold: π_r is defined as the fraction
797 of samples in which a particular variable must be observed to be considered stable.
798 We set π_r to 0.9, which means that a particular variable must be present in 90% of
799 resamples to be considered stable. The outcome of this stability selection procedure
800 is a set of stable features. A benefit of stability selection is that it is insensitive to
801 tuning parameters. Here, we simply set the L_1 penalty at $\sqrt{p}/2$, which is halfway
802 along the regularization path running from 1 to \sqrt{p} . It is worth noting that the stability
803 selection procedure is easily parallelizable here as it simply involves re-applying the
804 msCCA-regression algorithm to multiple different resamples of the same data.

805

806 **Analysis Design**

807 The L_1 penalty used in sCCA means that the parametric tests used for significance
808 testing in classical CCA (for example Wilk's Lambda)⁶³ cannot be used here,
809 necessitating the use of permutation testing to determine whether results are
810 significant. We assessed the in-sample significance of the results we obtained here,
811 then replicated these findings using an out-of-sample, hold-out set design. This kind
812 of experimental design has a number of advantages in the present context: using a
813 training/testing design, it is possible to obtain an unbiased estimate of effect size. We
814 used a hold-out set design in preference to a cross-validation procedure. This is
815 because cross-validation involves the training and testing of multiple statistical
816 models, one for each cross-validation fold, which precludes the use of a single model
817 for further validation/characterization. A related advantage is that it is possible to
818 carry out further characterization of the test set results, due to the fact that we are
819 able to estimate effect size in an unbiased way.

820 In detail, the analysis design was carried out as follows:

- 821 1) Psychiatric symptom data, and data from the VBM, TBSS and rs-fcMRI
822 neuroimaging modalities was extracted and transformed into $n_t \times p_i$ matrices,
823 where n_t is the number of participants included in the training dataset, and p_i
824 is the number of features included in each of the views of the data.
- 825 2) The full dataset was randomly split into training and testing sets. The training
826 set was made up of 70% of the data whilst the testing set was made up of the
827 remaining 30%.

828 3) The training data was then randomly split into a hundred further resamples.
829 Each resample was made up of $n_t/2$ participant scans, where n_t is the total
830 number of participants in the training dataset.

831 4) The first stage of the mSCCA- regression algorithm (see above) was then
832 applied to each resample, with a sparsity constraint of $\sqrt{p_i}/2$ in each view of
833 the data.

834 5) We then recorded which variables, in each view of the data, are present in
835 over 90% of resamples. These variables are considered to be stable, and are
836 retained.

837 6) We then re-applied the msCCA algorithm to the data, without sparsity
838 constraints, on the variables that survived more than 90% of resamples.

839 7) We then combined the neuroimaging canonical variates we found in the
840 previous step in a prediction model on the symptom canonical variate, using
841 ordinary least squares regression. We then recorded the correlation between
842 the neuroimaging prediction model, and the symptom canonical correlate.

843 8) We then permuted the training data, and repeated steps 3-7. This was done
844 for 10,000 different permutations of the training data labelling. In each case,
845 we recorded the correlation between the neuroimaging model, and the
846 canonical correlate of psychiatric symptoms. In this way, we built up a
847 permutation distribution to assess the significance of the relation between
848 symptom and neuroimaging data in the experimental labelling, within the
849 training dataset.

850 9) We then applied the trained model to the test set to produce canonical
851 correlates of symptom and neuroimaging measures. We recorded
852 associations for both the full model, and between the psychiatric symptom
853 score, and each of the individual neuroimaging canonical correlates.

854 10) We then randomly permuted the data rows in the testing set and re-
855 calculated correlation values between symptom and brain canonical
856 correlates. We recorded associations between psychiatric symptoms and the
857 full neuroimaging model, for each of 10,000 permutations of the experimental
858 labelling.

859 11) It is also interesting to find the significance of the individual neuroimaging
860 modalities. However, as we are testing the significance of multiple
861 neuroimaging modalities, it is necessary to correct for multiple comparisons
862 across these different modalities. This is easily done using the distribution of
863 the maximal statistic: for each permutation of the experimental labelling, we
864 calculate the association between the symptom score and each of the
865 neuroimaging canonical correlates; the largest of these associations is then
866 recorded. This is done for each of the 10,000 permutations of the test
867 labelling, producing a distribution of the maximal statistic. Correlations
868 between symptom and neuroimaging measures in the experimental labelling
869 are then significant at the FWE-corrected level α if they are above the $100*(1-$
870 $\alpha)$ percentile of this distribution.

871 This process is illustrated in Supplementary Figure 1.

872

873 **Confounds**

874 It is important to account for the effects of confounds, which might otherwise lead to
875 spurious relations between the different data views⁶⁴. Here, we regressed age,
876 gender, site and intracranial volume from all data views prior to the sCCA analysis⁶⁵⁻
877 ⁶⁷. For the connectivity measures derived from rsfMRI data, we also regressed the
878 mean between-volume fractional displacement, and the percent of slices corrupted
879 by artefacts, from the scans.

880 **Additional Analyses to Localise Effects**

881 We used msCCA-regression to find multivariate relations between psychiatric
882 symptomatology and neuroimaging measures of brain structure and function. In
883 using msCCA-regression, it is possible to make inferences on relations between sets
884 of psychiatric symptoms and neuroimaging measures across the brain, it is not
885 possible to make inferences on individual brain regions/connections or individual
886 questionnaire items. For this reason, we conducted additional analyses to further
887 deconstruct the relationship between psychiatric symptomatology and the brain. This
888 procedure is similar to a redundancy analysis^{68,69}. In particular, we were interested in
889 localising which brain regions exhibited an individually significant association with
890 psychiatric symptomatology.

891 Conducting further tests on the whole dataset would introduce circularity into the
892 analysis. Therefore, additional inference must be carried out on the testing dataset
893 alone. Nevertheless, the training dataset is still likely to contain useful information,
894 which can be used to guide analyses carried out on the testing dataset, thus
895 decreasing the multiple comparison problem, and increasing the likelihood of finding
896 significant effects in the testing dataset. In the present investigation, we looked for

897 significant localizable effects in the training dataset, we then used these results to
898 inform analyses carried out on the testing dataset. In this sense, the training dataset
899 was used as a 'discovery dataset'.

900 In the case of the TBSS and VBM data, we sought to localize associations between
901 symptoms and the brain to the cluster-wise level. In the case of the rs-fcMRI data,
902 we sought to localize changes to individual inter-regional connections. VBM and
903 TBSS clusters were defined using an 18-connectivity scheme. This means that
904 voxels must be connected by a face or an edge to be considered a part of the same
905 cluster.

906 This analysis was carried out in the manner described below:

- 907 1) We calculated the grey matter volume and FA in spatially distinct clusters
908 identified in the sCCA analysis applied to VBM and TBSS respectively. We
909 extracted connectivity values with non-zero canonical weights. This was done
910 in both the training and testing datasets.
- 911 2) We calculated Pearson's correlation coefficient between the mean of each
912 spatially distinct cluster/connection, and the sum of symptom score values.
913 This was done separately in the training and testing datasets.
- 914 3) Rows associated with neuroimaging data in the training set were permuted
915 and correlations between clusters/connections, and symptom clusters were
916 recalculated. The maximal value was recorded. Training data was permuted
917 10,000 times; the maximum correlation value across all clusters/connections
918 was recorded for each permutation. Clusters/connections exhibiting a
919 significant effect in the training dataset were then determined by comparing

920 correlation values to the distribution of the maximal statistic^{50, 51}. Because
921 model selection was carried out in the training dataset, conducting inference
922 on the training dataset would constitute “double dipping”.

923 4) Clusters/connections exhibiting a significant effect in the training dataset were
924 taken forward for an analysis carried out in the testing set.

925 5) We calculated correlation values between clusters/connections in the testing
926 dataset, and the symptom score.

927 6) Testing data was permuted 10,000 times; the maximum correlation value
928 across all clusters/connections was recorded for each permutation.

929 Clusters/connections exhibiting a significant effect in the testing dataset were
930 determined by comparing correlation values to the distribution of the maximal
931 statistic. Cluster/connection correlations in the testing dataset were then
932 compared to correlations in the distribution of the maximal statistic.

933 Cluster/connection correlations in the experimental labelling, which were in
934 the top 5% of the distribution of the maximal statistic, were considered
935 significant at the FWE corrected level.

936 This process is illustrated in Supplementary Figure 3.

937 **Finding Multiple Modes of Variation**

938 Using canonical correlation analysis, it is possible to uncover multiple modes of
939 variation between datasets. After determining the significance of the first canonical
940 correlate, we remove the effect of the first set of canonical vectors, and repeat the
941 analysis. Witten et al used Hotelling's deflation to remove the effect of the first vector;
942 this approach has been criticized by Monteiro et al, who propose the projection

943 deflation procedure as an alternative^{11,70}; this is the procedure we use in the present
944 investigation. Correlations between the different canonical relations are given in
945 Supplementary Table 6.

946 It is possible to ascertain the significance of all canonical relations after the first by
947 comparing the correlations of subsequent associations to the permutation distribution
948 of the first relation: The first canonical relation between sets is by definition the
949 strongest; any subsequent associations between sets will be weaker than the
950 canonical relation that preceded it. A common means of correcting for multiple
951 comparisons is to compare test statistics in the experimental labelling to the maximal
952 statistic across all tests in the permutation distribution; this distribution is usually
953 termed the distribution of the maximal statistic^{71,72}. In the present investigation, we
954 can find this distribution by recording the strength of the first canonical relation, for
955 each permutation. Significance values that are corrected for multiple comparisons
956 can then be found by comparing associations of subsequent modes of variation, with
957 this distribution⁷³.

958 **Hypothesis Driven Analysis**

959 A major advantage of the approach described here is that it allows the grouping of
960 psychiatric illnesses to be driven by their biological underpinnings. Nevertheless, it is
961 an open question whether the symptom groups discovered in the data driven
962 analysis we ran here show a stronger relation to neuroimaging measures of brain
963 structure and function than pre-defined symptom groups. For this reason, we tested
964 whether the widely used internalising/externalising organisation of psychiatric illness
965 is able to explain as much variance in psychiatric symptomatology as this purely data
966 driven method. To do this, we used an approach that is as similar as possible to the

967 primary data analysis followed in the main part of the investigation, yet still makes
968 use of the internalising/externalising illness structure: we replaced the symptom
969 matrices used in the main part of the investigation with symptom vectors based on
970 previously defined internalising and externalizing symptom sub-scales from the
971 DAWBA; no sparsity was applied to psychiatric symptom sub-scales. Used in this
972 manner, the msCCA-algorithm reduces to something like a sparse partial least
973 squares regression⁷⁴, where the neuroimaging features are predictors and the pre-
974 defined internalising/externalising vectors are the targets. This method was applied
975 twice, once to predict the internalising symptom dimension, and once to predict the
976 externalising. We term the internalizing and externalising symptom scales as
977 DAWBA-internalising and DAWBA-externalising respectively. We defined symptoms
978 as belonging to broad internalising or externalising categories in the same way as
979 Aebi et al⁷⁵ : The DAWBA-internalising scale was created by summing: specific
980 fears, social fears, panic attacks, stress after a frightening event, worrying and
981 depression. The DAWBA-externalising scale was created by summing: Attention and
982 activity, behaviours and attitudes that can get people into trouble, and Cigarettes,
983 Alcohol and Drugs sections of the DAWBA. The SDQ is already split into broad
984 internalising and externalising domains⁴⁵. Therefore, internalising and externalising
985 SDQ scores were simply added to these scores to create DAWBA-internalising and
986 DAWBA-externalising scores respectively. The sections: rapidly changing mood,
987 dieting and bingeing and strange experiences that are surprisingly common were not
988 used to create scores as these symptoms do not fit neatly into an
989 internalising/externalising dichotomy. All of these questions can be found in
990 Supplementary Table 1.

991

992 **Longitudinal Analysis**

993 The msCCA-regression analysis described above was used to find relations between
994 psychiatric symptoms and neuroimaging measures of brain structure at age 19,
995 when participants were young adults. However, the developmental time period
996 immediately preceding this time point is also of potential interest, with the brain going
997 through important maturational processes and participants being at increased risk for
998 the development of psychopathology⁷⁶. Thus, we applied the msCCA-regression
999 algorithm between psychiatric symptoms and neuroimaging measures at age 14.
1000 The results of this analysis are show in Supplementary Figure 8. We did not find a
1001 significant relation between psychiatric symptoms and the brain at this age. As rs-
1002 fMRI data is only available for a small sub-sample of the full dataset at age 14, we
1003 only used VBM and TBSS data in this analysis.

1004 It is possible that neuroimaging markers of psychiatric illness precede the
1005 development of full-blown psychiatric symptomatology. To determine whether this
1006 was the case in the present investigation, we took the TBSS and VBM regions
1007 identified as being associated with psychopathology at age 19, we then extracted the
1008 appropriate neuroimaging data from these brain regions at age 14, and correlated
1009 the output with symptoms at age 19. In this way, we showed that neuroimaging
1010 measures at age 14 have predictive value for psychopathology at age 19.

1011 For these analyses, we used the same subjects as were included in our
1012 analysis at age 19. We also used the same train-test split within this subject group.
1013 We subjected this age 14 data to the same QC procedures as the data taken at age
1014 19. Of the n = 666 subjects used in the msCCA-regression analysis carried out at
1015 age 19, 72 subjects had data that did not pass QC at age 14. This left n = 594

1016 subjects for age 14 analyses, with $n = 412$ subjects in the training group and $n = 182$
1017 in the testing/replication group.

1018 **Clinical Analyses**

1019 Using mSCCA-regression, we found a set of neuroimaging features that correlate
1020 with a set of questions assessing psychiatric health. At the group level, participants
1021 who score more highly on the vector derived from neuroimaging data will suffer a
1022 larger number of psychiatric symptoms (as measured by the DAWBA). It might
1023 therefore be expected that participants with a clinical diagnosis of a psychiatric
1024 disorder would score more highly on this neuroimaging vector than healthy controls.
1025 To discover whether this was the case, we subjected clinical data to exactly the
1026 same pre-processing as the IMAGEN data; we then looked for changes in grey
1027 matter volume in the regions identified in the initial analysis. A (one-sided) two-
1028 sample t-test was used to determine whether patients and controls differed
1029 significantly on this one-dimensional measure. We only used grey matter data here
1030 as this data-type showed the strongest relation to psychopathology in the IMAGEN
1031 sample. Furthermore, this data-type is widely available and the number of degrees of
1032 freedom in the MRI scan acquisition parameters is low. The case-control tests we
1033 used here make the assumption of data normality, although this was not formally
1034 tested here.

1035 We used the same confounds in this analysis as we did on the IMAGEN data, this
1036 includes the use of total grey matter as a covariate of no interest. However, it could
1037 still be argued that regional changes are only acting as a proxy for total grey matter.
1038 In order to determine whether this is the case, we repeated all pertinent analyses,

1039 using total grey matter as a regressor in addition to total intracranial volume. The
1040 results of these analyses are shown in Supplementary Figure 10.

1041

1042 **Depression sample**

1043 The Munich sample consisted of patients with first episode and recurrent unipolar
1044 Depression treated as in-patients at the Max Planck Institute of Psychiatry, Munich,
1045 and healthy control participants. The data for 13 of the participants assessed was not
1046 used as it was deemed to be of insufficient quality, this left: N=614; 400 patients, age
1047 48 [SD 13.8] years, 53% women; 214 control participants age 49 [SD 13.3] years,
1048 58% women, for the most part overlapping with imaging genetic and MDD
1049 association studies reported in collaboration with the ENIGMA consortium^{22,77}. Other
1050 than in the two flagship studies, no bipolar patients were included for reasons of
1051 clinical homogeneity. MDD diagnoses were based on clinical consensus in addition
1052 to M-CIDI or SCAN interviews, depending on the original study protocols. The
1053 Munich sample comprised images acquired in subsamples of the Munich
1054 Antidepressant Response Signature Study and the Recurrent Unipolar Depression
1055 Case-Control study, both performed at the MPIP. We did not use any statistical
1056 analyses to decide on the sample size used here. However, the sample used was
1057 among the largest of any single study investigating alterations in brain structure in
1058 depressed participants⁷⁷.

1059 **Schizophrenia/Bipolar sample**

1060 Participants with schizophrenia and bipolar disorder were recruited from the
1061 Thematically Organised Psychosis (TOP) study. This is a collaborative study based
1062 at the University of Oslo in Norway. The data for 2 participants was not used as it

1063 was considered to be of insufficient quality, this left: 286 Controls (aged 34 [SD 9.5]
1064 years, 46% women), 161 Schizophrenics (aged 32 [SD 8.8] years, 35% women) and
1065 189 participants with Bipolar Disorder (aged 34 [SD 11.5] years, 58% women).
1066 Patients were recruited from the psychiatric unit of Oslo University Hospital and were
1067 assessed for psychiatric illness with the Structural Clinical Interview for DSM-IV Axis
1068 I disorders (SCID-I). This assessment was either administered by an MD, or a
1069 clinically trained psychologist, and was used to assess the presence of AXIS I
1070 disorders. Before participation, control participants were screened to exclude serious
1071 somatic and psychiatric illness, substance abuse, or MRI-incompatibility. All
1072 participants gave written informed consent before participation. Further information
1073 about this sample and the scan protocols used can be found in Rimol, L. M. et al⁷⁸.
1074 We did not use any statistical methods to pre-define the sample size used in this
1075 investigation. Nevertheless, the sample used is among the largest of any
1076 investigating structural brain alterations in Schizophrenia⁷⁹ and Bipolar disorder⁴¹

1077 **ADHD sample**

1078 Data for the ADHD sample was taken from the NeuroIMAGE project, a clinical cohort
1079 study. The study is made up of individuals tested at two different sites in the
1080 Netherlands, The Donders Centre for Cognitive Neuroimaging in Nijmegen, and the
1081 Vrije Universiteit in Amsterdam. The total sample consisted of 184 participants
1082 suffering from ADHD, 103 unaffected siblings, and 128 healthy controls. Further
1083 information on the participants and the protocols used can be found in von Rhein et
1084 al⁸⁰. This sample includes a number of very young participants, which is likely to
1085 introduce a large degree of heterogeneity into the analysis. For this reason, we did
1086 not analyse the data from participants under the age of fifteen. This age divide point

1087 was considered to offer a reasonable trade-off between sample homogeneity and
1088 size. The data for 12 of the participants was not used as it was deemed to be of
1089 insufficient quality. Case-control Analyses were made between 74 healthy controls
1090 (aged 18 [SD 2.0] years, 50% women) and 131 ADHD participants (aged 18 [SD 2.3]
1091 years, 27% women). No formal statistical methods were used to determine the size
1092 of this sample. However, this sample is large compared to similar samples
1093 investigating case-control differences in brain structure in patients with ADHD⁸¹.

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1099 **Data Availability Statement**

1100 IMAGEN data used in this investigation will be made available upon reasonable
1101 request to the corresponding author. All other data is available upon reasonable
1102 request addressed to the appropriate study leads.

1103

1104 **Code Availability Statement**

1105 The core code used to run the analyses reported in this study are available as
1106 Supplementary Software. Supporting code can be found at:
1107 <https://github.com/alexjamesing/mscca-regression-code>.

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1340 **Author Contributions**

1341 **Author Contributions**

1342 **Pre-processed data:** AI, CC, IMV, PGS, HL, TJ, GR; **Analysed the data:** AI, PGS; **Wrote the manuscript:**
1343 AI, GS, FB, PGS; **Conceptualised the study:** AI, GS, TWR, AM, JA, EB; **Collected Data:** NT, EBQ, TW,
1344 SD, TB, ALWB, UB, CB, PC, TF, HF, VF, HG, PS, PG, YG, AH, BI, VK, JLM, AML, SB, FN, BVN, DPO, MLPM,
1345 SM, JP, LP, MS, AS, MNS, HW, RW, OAA, IA, EDB, JB; **Prepared Figures:** AI, NT **Revised Manuscript:**
1346 All Authors

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1348 **Competing Interests**

1349 Dr. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim
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1360 interests or potential conflicts of interest.

1361 *Figure 1: Results of the first msCCA-regression analysis showing relations between*
1362 *anxiety/depression psychiatric symptoms and neuroimaging measures in the IMAGEN sample. (a):*
1363 *The full msCCA-regression model linking psychiatric symptoms to VBM, TBSS and rs-fcMRI*
1364 *neuroimaging measures at age 19. We found associations between psychiatric symptoms and*
1365 *neuroimaging measures of $r = 0.59(465)$ ($p < 0.001$) in the training set, and associations between*
1366 *symptoms and the brain of $r=0.23(197)$, $p<0.001$, 95% CIs= $0.13, \infty$ in the test set; (b): Shows the*
1367 *msCCA-regression model linking psychiatric symptoms with the different neuroimaging measures (c):*
1368 *Psychiatric symptoms contributing to this relation are shown on the left, their canonical weights are*
1369 *shown in red. (d): rs-fcMRI measures of functional connectivity. (e): VBM measures of grey matter*
1370 *volume associated with symptoms. (f): TBSS measures of fractional anisotropy (FA).*

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1372 *Figure 2: Results of the second msCCA-regression analyses showing relations between executive*
1373 *dysfunction symptoms and neuroimaging measures in the IMAGEN sample, following the removal of*
1374 *the first canonical relation. (a): The full msCCA-regression model linking psychiatric symptoms to*
1375 *VBM, TBSS and rs-fcMRI neuroimaging measures at age 19. We found associations between*
1376 *executive dysfunction symptoms and neuroimaging measures of $r = 0.46$ ($p = 0.004$) in the training*
1377 *set, and associations between symptoms and the brain of $r = 0.19(197)$, $p = 0.002$, 95% CIs = $0.087,$
1378 ∞ in the test set; (b) msCCA-regression model linking psychiatric symptoms with the different
1379 neuroimaging measures (c) Symptoms contributing to this relation are shown on the left their
1380 canonical weights are shown in red. (d) rs-fcMRI measures of functional connectivity. (e) VBM*

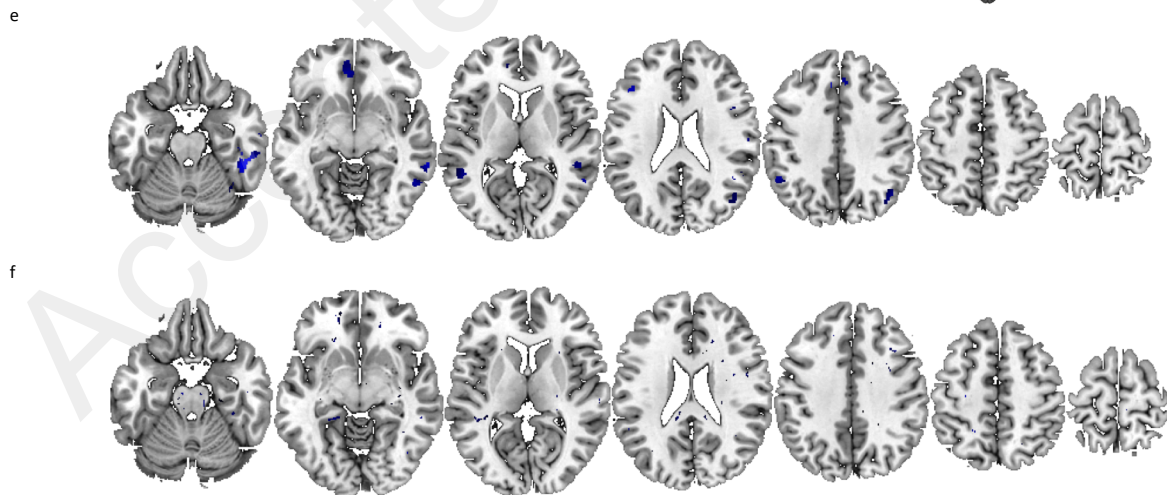
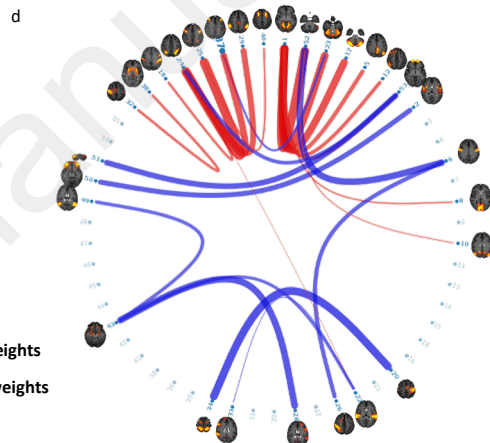
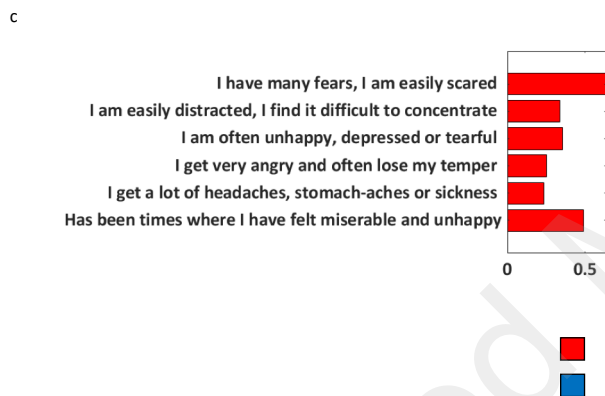
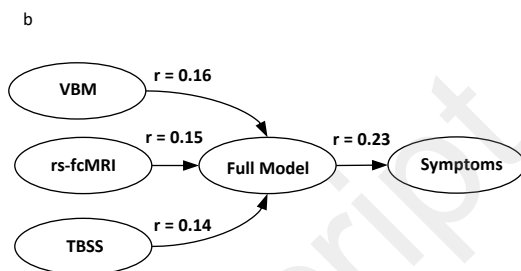
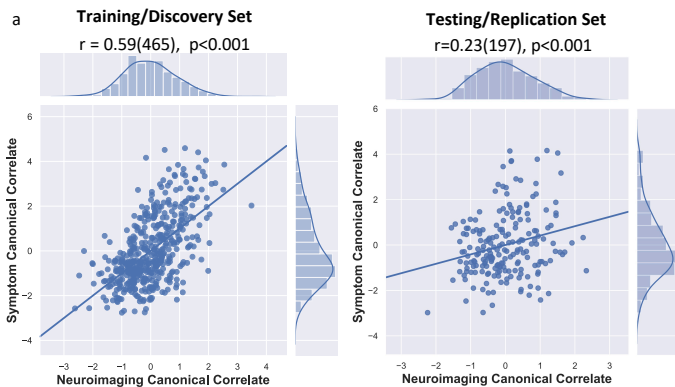
1381 measures of grey matter volume associated with symptoms. (f): TBSS measures of fractional
1382 anisotropy (FA).
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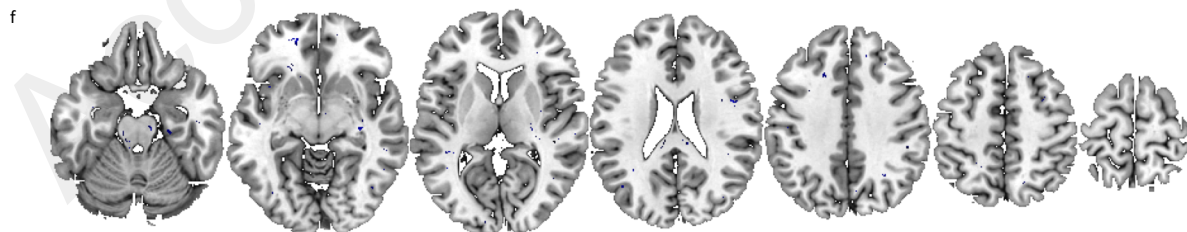
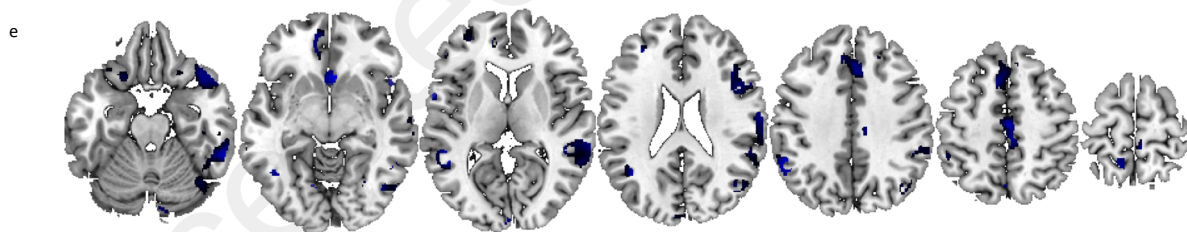
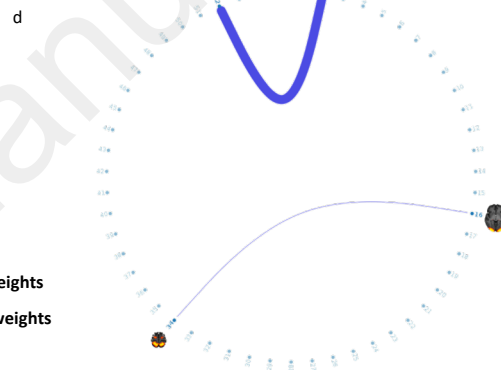
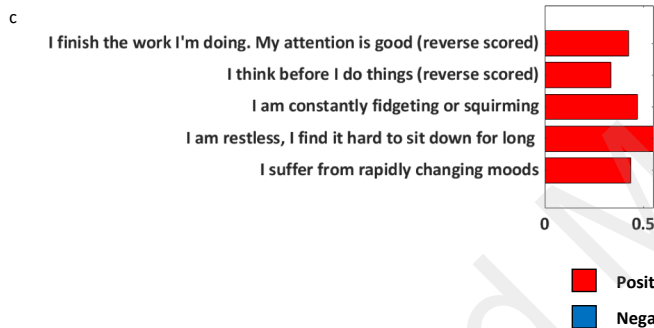
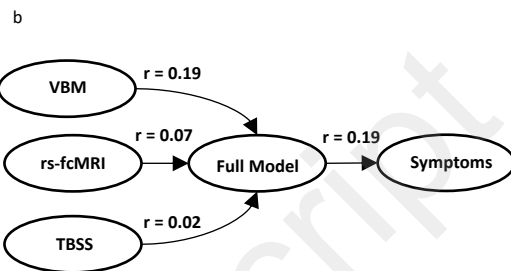
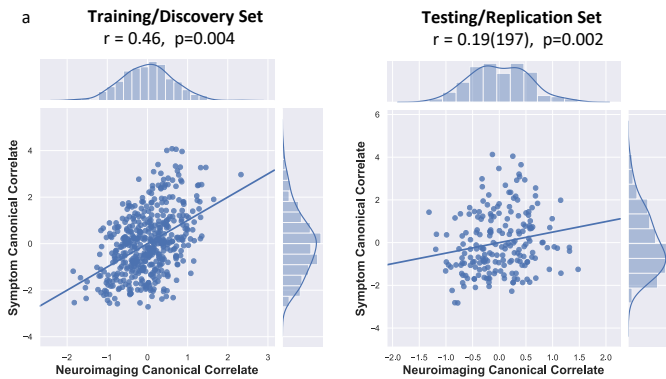
1384 *Figure 3: Longitudinal analysis of canonical correlates. (a) anxiety/depression symptom correlates:*
1385 *VBM and TBSS brain correlates established at age 19 are associated with anxiety/depression*
1386 *behavioural symptoms at age 19 ($r = 0.19(180)$, $p = 0.003$, 95% CIs= $0.069, \infty$), but not at age 14*
1387 *($r=0.020(180)$, $p=0.40$, 95% CIs= $-0.10, \infty$). Brain correlates at 14 years predict the manifestation of*
1388 *behavioral symptoms at 19 years ($r=0.14(180)$, $p=0.023$, 95% CIs= $0.022, \infty$). (b) Executive*
1389 *dysfunction symptom correlates: VBM and TBSS correlates established at age 19 are associated with*
1390 *behavioral symptoms at age 19 ($r = 0.15(180)$, $p = 0.024$, 95% CIs= $0.028, \infty$), but not at age 14*
1391 *($r=0.030(180)$, $p=0.41$, 95% CIs= $-0.093, \infty$). Brain correlates at 14 years do not predict the*
1392 *manifestation of behavioral symptoms at 19 years ($r=0.11(180)$, $p=0.065$, 95% CIs = $-0.010, \infty$).*

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1395 *Figure 4: Differences in the grey matter correlates of anxiety/depression and executive dysfunction*
1396 *psychiatric symptoms, between cases and controls for a range of psychiatric illnesses. For the box*
1397 *and whisker plots, the central mark in each box represents the median, with the top and bottom edges*
1398 *of the box indicating the 25th and 75th percentiles of the sample respectively, whiskers represent 1.5x*
1399 *the interquartile range and the hollow circles represent sample outliers. For display purposes, total*
1400 *grey matter in each case-control comparison is divided by the pooled standard deviation. The effect*
1401 *sizes (calculated using Cohen's D) relating to these differences are shown in the right-hand panel. (a):*
1402 *Differences in grey matter volume between patients and controls in the anxiety/depression set of grey*
1403 *matter correlates are shown in the left-hand panel. Clinical psychiatric disorders exhibited the*
1404 *following case-control differences: Depression: t -statistic= $4.61(612)$, $p < 0.001$, Cohen's $D = 0.39$, 95%*
1405 *CIs= $0.25, \infty$; Schizophrenia: t -statistic= $2.54(445)$, $p=0.002$, Cohen's $D=0.25$, 95% CIs = $0.087, \infty$;*
1406 *ADHD (t -statistic= $1.84(203)$, $p=0.034$, Cohen's $D=0.26$, 95% CIs= $0.030, \infty$; Bipolar: (t -statistic= $-$*
1407 *$0.23(473)$, $p=0.59$, Cohen's $D=-0.02$, 95% CIs= $-0.17, \infty$). (b): Differences in grey matter volume*
1408 *between patients and controls in the executive dysfunction set of grey matter correlates. Clinical*
1409 *psychiatric disorders exhibited the following case-control differences: Depression: t -*
1410 *statistic= $1.65(612)$, $p=0.050$, Cohen's $D=0.14$, 95% CIs= $0.001, \infty$, Schizophrenia: t -*
1411 *statistic= $2.81(445)$, $p=0.0026$, Cohen's $D=0.28$, 95% CIs= $0.11, \infty$; ADHD: t -statistic= $2.19(203)$,*
1412 *$p=0.014$, Cohen's $D=0.32$, 95% CIs= $0.070, \infty$; Bipolar: t -statistic= $-1.33(473)$, $p=0.90$, Cohen's $D=-$*
1413 *0.12 , 95% CIs= $-0.27, \infty$.*

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a.

Anxiety/Depression

$r = 0.19(180), p = 0.003$

Age 19

Symptoms

Neuroimaging

$r = 0.14(180), p = 0.023$

Age 14

Symptoms

Neuroimaging

$r = 0.020(180), p = 0.40$

b.

Executive Dysfunction

$r = 0.15(180), p = 0.024$

Symptoms

Neuroimaging

$r = 0.11(180), p = 0.065$

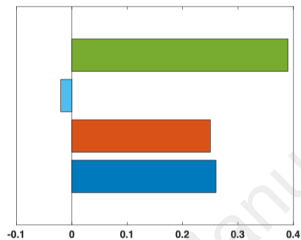
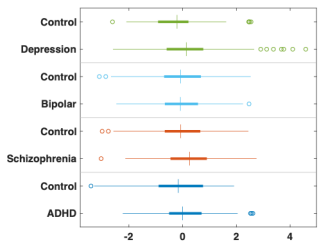
Symptoms

Neuroimaging

$r = 0.030(180), p = 0.41$

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a.



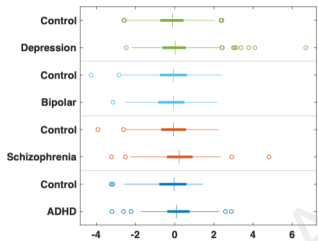
t-statistic=4.61(612), $p < 0.001$, Cohen's D = 0.39

t-statistic=-0.23(473), $p = 0.59$, Cohen's D=-0.02

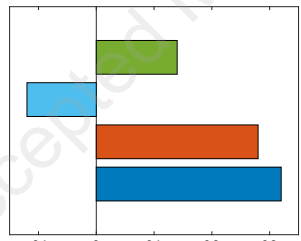
t-statistic=2.54(445), $p = 0.002$, Cohen's D=0.25

t-statistic=1.84(203), $p = 0.034$, Cohen's D=0.26

b.



Normalised Grey Matter



Cohen's D

t-statistic=1.65(612), $p = 0.050$, Cohen's D=0.14

t-statistic=-1.33(473), $p = 0.90$, Cohen's D=-0.12

t-statistic=2.81(445), $p = 0.0026$, Cohen's D=0.28

t-statistic=2.19(203), $p = 0.014$, Cohen's D=0.32