Unpacking the functional heterogeneity of the Emotional Face Matching Task: a normative modelling approach

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Abstract:

In this study we dissect the heterogeneity that underlies traditional group-level analyses, and determine how individualised patterns of predicted activation relate to age, sex, and variations in acquisition parameters and task design choices. To this end we take advantage of six large open-access/shared datasets and collate a large representative sample of over 7500 participants from which we build a normative of task-evoked activation during a widely used emotional reactivity task, the Emotional Face Matching Task. This enables us to bind heterogeneous datasets to a common reference model and enables meaningful comparisons between them. We then apply this model to the naturalistic and clinically realistic MIND-Set cohort, which is a heterogeneous and highly comorbid sample containing individuals with one or more current diagnosis (affective and anxiety disorders, autism spectrum disorders and/or attention deficit hyperactivity disorder). This enables us to determine whether, and if so how, participants with mental illness and/or neurodivergence differ from the reference cohort, both at the group level and at the level of the individual and in terms of cross-diagnostic symptom domains in addition to diagnosis. We show that patients have, on average, a higher frequency of extreme deviations, and have unique spatial distributions depending on the DSM-IV diagnosis and the number of co-occurring diagnoses when models are constructed using the face>shapes task contrast. Models built using the face>baseline task contrast, have, by comparison, greater predictive value for individuals' functioning across four transdiagnostic domains. We demonstrate the application of the normative modelling framework to task-based functional neuroimaging data, discuss its potential to further our understanding of individual differences in brain function within reference populations, and further validate the clinical relevance of these models.

Introduction:

Task-based functional neuroimaging (functional magnetic resonance imaging; fMRI) has been widely applied in foundational and clinical neuropsychology to characterise neural processes that underpin a behaviour or process of interest. The typical approach in such studies is based on comparing mean differences in the magnitude and location of activation (measured by changes in BOLD signal), which has helped us to understand how these processes may differ between groups defined by biological and sociocultural factors, psychopathologies, or therapeutic interventions. The majority of prior research has reported group-level summary statistics, which inform us of those regions most consistently activated across participants/groups during task conditions. This method assumes that the neural mechanisms facilitating the process of interest are consistent across individuals within and between groups. This assumption enables our understanding to reach only so far as 'the average brain' of an 'average control', or 'average patient'.

In order to better understand how the brain relates to behaviour it is essential move our focus from the group-level to studying individual differences and consider the neural activation of these processes within the context of multiple sources of heterogeneity. For example: (i) natural variation within the general population, including potentially heterogenous yet functionally convergent processes, and (ii) heterogeneity within groups of interest, such as within mental health diagnoses. Furthermore, when comparing between independent studies, the influence of task design (i.e. small modifications to an original task) and acquisition parameters should also be considered but are seldom investigated.

One approach that can provide insight into individual differences is normative modelling[1, 2]. The normative modelling framework provides statistical inference at the level of each subject with respect to an expected pattern across the population, highlighting variation within populations in terms of the mapping between biological variables and other measures of interest. This framework has previously been employed by our group and others to dissect structural variation within large healthy populations[3] and clinical psychiatric populations (e.g. in autism [4-6], schizophrenia and bipolar disorder[7]), and in relation to dimensions of psychopathology[8]. Applying this method to task-based fMRI data we will be able to characterize how functional activity within each voxel or ROI in the brain differs between individuals, and hence show with greater nuance the range of task-evoked activation within the general population[2]. Further, applying this model to patients with a current diagnosis (affective and anxiety disorders, autism spectrum disorders (ASD) and/or attention deficit hyperactivity disorder (ADHD)) we will be able to map differences in these individual participants with respect to the reference cohort. This may reveal unique clusters of deviation patterns, within and/or across diagnostic categories.

In this study, we use the Emotional Face Matching Task (EFMT) to demonstrate the potential of the normative modelling method to identify individual differences in task-based fMRI. The EFMT, also commonly referred to as the 'Hariri task', has been used in over 250 fMRI studies since it was most notably introduced in 2002[9, 10]. This task asks participants to match one of two images that are simultaneously

presented at the bottom of the screen, to a third target image displayed at the top of the screen; participants match images of facial configurations consistent with the common view of prototypic facial expressions, most frequently of fear or anger, or similarly positioned geometric shapes. Matching faces, as compared to matching shapes, evokes explicit and/or implicit emotional face processing, which has previously been shown to engage the amygdala, fusiform face area, anterior insula cortex, the pregenual and dorsal anterior cingulate cortex, the dorsomedial and dorsolateral prefrontal cortex, and visual input areas. Previous work has related activity to biological and demographic variables, and compared between many different clinical groups and developmental spectrums.

Due to its experimental simplicity and focus on subcortical circuitry relevant to brain disorders, the EFMT has been implemented in a number of large-scale neuroimaging initiatives including the UK Biobank[11], the Human Connectome Project (HCP)[12, 13], HCP Development[14], the Amsterdam Open MRI Collection Population Imaging of Psychology (AOMIC PIOP2)[15], and the Duke Neurogenetics Study (DNS). We take advantage of these large open-access/shared datasets to collate a large representative sample of over 7500 participants to first (1) build reference normative models that highlight the natural variation of functional activity evoked by the EFTM [as measured by the task contrasts faces > shapes and faces>baseline], and (2) determine how the model's prediction relates to age, sex, and variations in task design. We then apply these models to over 200 participants with a current mental health condition or who are neurodivergent from the MIND-Set cohort (Measuring Integrated Novel Dimensions in neurodevelopmental and stress-related psychiatric disorder)[16], to (3) determine whether, and if so how, patients with a current diagnosis (affective and anxiety disorders, ASD and/or ADHD) differ from the reference cohort, both at the group level and at the level of the individual. We show that despite the ostensible simplicity of this task and robust group effects, there is considerable inter-individual heterogeneity in the nature of the elicited activation patterns and that such differences are both highly interpretable and predict cross-domain symptomatology in a naturalistic clinical cohort.

Methods:

Data sets: We collated a large reference sample from 6 independent sites for whom high quality fMRI data for the EFMT are available: AOMIC PIOP2, Duke Neurogenetics Study, HCP Development, HCP Young Adult (1200 release), UK Biobank, and the MIND-Set cohort which also includes a clinical population. For sample details per site see Table 1.

fMRI task paradigms: All sites collected a variant of the EFMT[9]. Although specific parameters varied, the overall design was consistent: in each face trial participants were presented with three images of human faces in a triangular formation. Participants were instructed to identify which of two faces/expressions presented at the bottom of the screen matched the one presented at the top of the screen by pushing a button with the index finger of their left or right hand. Multiple face trials were presented in one face block,

and the task included multiple face blocks (see Table 1 for the number of trials per block, and number of blocks per site). As a somatomotor control, participants also completed shape trials, wherein they were presented with three geometric shapes (circles and ovals) and asked to indicate which of the two shapes presented at the bottom of the screen matched the one at the top. Multiple shape trials were concatenated to form one shape block, which were interspersed between face blocks.

Two paradigms (HCP Young Adult and HCP Development) included an inter-trial interval (white fixation cross on black screen), and three sites (HCP Young Adult, HCP Development and AOMIC PIOP2) had an instruction trial that preceded the start of each block. Tasks varied in their duration from 150 to 290 seconds, which indirectly corresponded to the acquisition of between 135 and 336 functional volumes.

fMRI data acquisition:

Site specific acquisition parameters per site are detailed in Table 1, and in the following site specific protocols: AOMIC PIOP2[15], HCP Young Adult[13], HCP Development[17], UKBiobank[18], Duke Neurogenetics Study (https://www.haririlab.com/methods/amygdala.html) and MIND-Set[19].

fMRI pre-processing: Data pre-processing was harmonised across all sites; a FSL-based pipeline[20] was consistently applied to decrease the likelihood of introducing variance due to pre-processing differences. Since the HCP young adult, HCP development and UKB Biobank data were already processed relatively consistently, we reused the processing pipelines provided by the respective consortia (for HCP sites we used the minimal processing pipeline)[18, 21] , with additional steps taken as necessary (e.g. matching smoothing kernels across studies). At a within-subject level, all functional data underwent gradient unwarping, motion correction, fieldmap-based EPI distortion correction (where fieldmaps were available), boundary-based registration of EPI to structural T1-weighted scan, denoising for secondary head motion-related artifacts using automatic noise selection, as implemented in ICA-AROMA[22], non-linear registration into MNI152 space, and grand-mean intensity normalization. All data were spatially smoothed using a 5 mm FWHM Gaussian kernel.

Quality control: Participants were excluded if their mean relative RMS was greater than 0.5mm. Additional quality control was performed for signal coverage in the prefrontal cortex for the UK Biobank sample (see supplementary methods).

fMRI general linear modelling (GLM) – single subject: We matched the methodological approach used to estimate the parameters within a GLM-based analysis, given evidence to suggest this analytic step can significantly contribute to the variability of reported results between sites[23]. Therefore, for each site, the linear model parameter were estimated using the FSL software package version 6.03 (HCP Young Adult, HCP Development, MIND-Set, Duke Neurogenetics Study; http://fsl.fmrib.ox.ac.uk/) or as downloadable form UK Biobank[18]. Two regressors were constructed from the faces and shapes blocks which were then

convolved with a canonical double-gamma haemodynamic response function and combined with the temporal derivatives of each main regressor. These were treated as nuisance regressors and served to accommodate slight variations in slice timing or in the haemodynamic response. Data were pre-whitened using a version of FSL-FILM customized to accommodate surface data, the model and data were high-pass filtered (200s cut-off). Fixed-effects GLMs were estimated using FSL-FLAME 1: first for independent runs, then when necessary combining two runs into a single model for each participant (HCP Young Adult). and the AOMIC, DNS and MIND-Set maps were transformed into standard space using FNIRT[24]. We created summary group level maps per site (for a random sample of 100 participants), as a sanity check to ensure the data was otherwise comparable to past literature, and performed a case-control comparison between patients with a current diagnosis (affective and anxiety disorders, ASD and/or ADHD) and unaffected controls in the MIND-Set cohort.

Normative models: The z-statistic maps from the contrast face>shapes (5mm smoothed in standard space), for each subject, were used as response variables for the normative models. That is, we specified a functional relationship between a vector of covariates and responses. We created normative models of EFMT-related BOLD activation maps, as a function of sex, age, acquisition and task parameters (task duration (s), number of target blocks, instructions given to participants, the task stimuli), by training a Bayesian Linear Regression (BLR) model to predict BOLD signal for the faces>shapes contrast. Generalisability was assessed by using a half-split train-test sample (train: n = 3877, test: n = 3764). In preliminary analyses, we compared a warped model which can model non-Gaussianity with a vanilla Gaussian BLR model. Since the fit was comparable across most metrics and regions, we focus on the simpler Gaussian model below. We included dummy coded site-related variables as additional covariates of no-interest. We also created models to predict BOLD signal for the faces condition alone (i.e. face>baseline contrast). This was performed in the Predictive Clinical Neuroscience toolkit (PCNtoolkit) software v0.26 (https://pcntoolkit.readthedocs.io/en/latest) implemented in python 3.8.

Quantifying voxel-wise deviations from the reference normative model: To estimate a pattern of regional deviations from typical brain function for each participant, we derived a normative probability map (NPM) that quantifies the voxel-wise deviation from the normative model. The subject-specific *Z*-score indicates the difference between the predicted activation and true activation scaled by the prediction variance. We thresholded participant's NPM at Z = ±2.6 (i.e. $p < .005$)[7] using fslmaths and summed the number of significantly deviating voxels with each participant, and then across the total sample.

Effects of input variables on model predictions: In order to probe the magnitude of the influence of task design parameters on the predicted BOLD signal, we illustrated the structure coefficients (correlation coefficients) of each task parameter-related variable (task duration (s), number of target blocks, instructions

given to participants, the task stimuli), as well as for age, sex and ICV. This approach is preferable to regression coefficients when variables are collinear[25].

Clinical application: We tested the normative models we created using the reference data, with a heterogeneous patient sample from the MIND-Set cohort (n = 236, mean age = 37. 1±13.27; 41.94% female). This is a naturalistic and highly co-morbid sample derived from out-patients of the psychiatry department of Radboud University Medical Centre. This included 150 patients diagnosed with a current mood disorder (unipolar or bipolar depressive disorder), 12 with generalised anxiety disorder, 22 with social phobia, 14 with panic disorder, 71 with attention-deficit-hyperactive-disorder, and 55 autistic individuals (see Table 1 for full details and note that subjects can be in multiple diagnostic categories). The clinical relevance of our models can also be tested in the context of transdiagnostic symptom domains; a conceptualisation of mental functioning that transcends diagnostic boundaries and allows for nuanced brain-behaviour interpretations. As such, for 217 (of our 236) patients for whom all required data was available, we repeated a previously validated factor analysis method (performed in SPSS v24.0, oblique rotation)[26] to obtain individual factor loadings on 4 functional domains: (1) negative valence, (2) cognitive function, (3) social processes and (4) arousal/inhibition.

Quantifying patients' voxel-wise deviations from the reference normative model: As for the reference cohort, we generated NPMs to estimate the pattern of regional deviations from typical brain function for each participant, and summed across the sample. We then used a Mann-Whitney U test to compare the frequency of deviations (>±2.6) between the reference controls and patients from the MIND-Set cohort.

Relating deviations to transdiagnostic functional domains: In order to map the association of the deviation scores with cross-diagnostic symptomatology, we performed sparse canonical correlation analyses (SCCA) to relate participant's scores in the four aforementioned functional domains or their diagnoses, to their whole-brain (unthresholded) deviation maps using an established penalised CCA framework that enforces sparsity[27, 28]. Specifically, we applied variable shrinkage by adding an l_1-norm penalty term to stabilise the CCA estimation and ensure the weights for the deviation scores were more interpretable. We follow the formulation outlined in WittenTibshirani (2009), where we refer to for details. In brief, given two data matrices $\boldsymbol{X}$ and $\boldsymbol{Y}$ with dimensions $n \times p$ and $n \times q$ respectively (here, these are the cross-diagnostic factor loadings and whole-brain deviations), and two weight vectors $\boldsymbol{u}$ and $\boldsymbol{v}$ this involves maximising the quantity $\rho = \boldsymbol{u}^{\boldsymbol{T}}\boldsymbol{X}^{T}\boldsymbol{Y}\boldsymbol{v}$ subject to the constraints $\|\boldsymbol{u}\|_2^2 \leq 1$, $\|\boldsymbol{v}\|_2^2 \leq 1$, $\|\boldsymbol{u}\|_1 \leq c_1$ and $\|v\|_1 \leq c_2$, where the penalties $p(\boldsymbol{u})$ and $p(\boldsymbol{v})$ are the standard L1-norm. We set the regularisation parameters for each view heuristically ($c_1 = 0.9p$ corresponding to light regularisation for the factor scores, $c_1 = 0.1q$, corresponding to heavy regularisation for the deviation maps such that no more than 10% of voxels were selected). While it is possible that better performance would be obtained by optimising the regularisation parameters across a grid, we did not pursue that here due to the moderate sample size for the clinical

dataset. We assessed generalisability of SCCA by splitting the data in to 70% training data and 30% test 10 times. Finally, we wrapped the entire procedure in a permutation test where we randomly permuted the rows of one of the matrices 1000 times to compute an empirical null distribution for significance testing.

Spatial patterns of deviations by primary and co-occurring diagnosis: We illustrated the spatial heterogeneity in deviations between different diagnoses (note that subjects can be in multiple categories), and further, compared patients with a single diagnoses to those with two, three, or more than three diagnosis, to determine whether and if so, how the location of deviations related to the number of co-occurring diagnoses a patient has.

Table 1: Sample details, functional scan acquisition parameters and Emotional Face Matching Task parameters for data included in the normative models.

Sample details				Functional scan acquisition parameters				Emotional Face Matching Task parameters									
Site	**Sample size**	**Sex**	**Age (mean+ S.D) [range]**	**Scanner**	**TE/TR (ms)**	**Multi-band Factor**	**Flip angle**	**Matching Rule /Instructions**	**Target Stimulus**	**Trials per block/ Blocks/ Total Trials**	**Trial duration (s)**	**Instruction duration (s)**	**Inter-trial interval (s)**	**Block duration (s)**	**Task duration (s)**	**Inter-block-interval (s)**	**Volumes acquired**
Human Connectome Project Young Adult	1044	561 F (53.7%)	28.76±3.70 [22-37]	3T Siemens Skyra	33.1/720	8	52	*Match faces*: Decide which of two faces presented on the bottom of the screen match the face at the top of the screen.	Angry and fearful faces: Nim-Stim Face Stimulus Set	6/3/18	2	3	1	21	156	NA	176
Human Connectome Project Development	201	110 F (54.7%)	13.86±3.83 [8-21]	3T Siemens Prisma	37/800												178
UK Biobank	5000	2487 F (49.7%)	63.99±7.45 [46- 82]	3T Siemens Skyra	39/735			*Match faces*: Indicate which face [or shape] on the bottom row matches the face on the top row.		NA/5/NA	NA	NA	NA		253	8	366
Amsterdam Open MRI Collection Population Imaging of Psychology	200	114 F (57.0%)	22.16±1.79 [18.25–26.25]	3T Phillips Achieva dStream	28/2000	NA	76.1	*Match expression*: Match the emotional expression of the target face as quickly as possible.		6/4/24	when selected or up to 4.8s	10	5s – Reaction Time	~25	290	5	135
Duke Neurogenetics Study	1246	707 F (56.7%)	20.22±1.21 [18.09-23.07]	3T GE MR750	30/2000		NA	*Match faces*: Decide which of two faces presented on the bottom of the screen match the face at the top of the screen.	Angry, fearful, surprised, neutral faces: Ekman and Friesen, 1976		4	2	Faces: 2–6 (mean= 4) Shapes: 2	Faces: 48 Shapes: 36	390	NA	195
MIND-Set	Reference: 37/309 Clinical Test: 36/309	21 F (56.7%) 21 F (58.3%)	38.0±16.11 [20-74] 37.1±16.50 [20-70]	3T Siemens Magentom Prisma	34/1000		60	*Match expression*: Indicate which one of the bottom two faces matched the top face in terms of emotional expression.	Angry and fearful faces: Nim-Stim Face Stimulus Set	6/2/12	5	NA	NA	30	150	NA	150
Additional details of clinical samples:	**Sample size**	**Sex**	**Age (mean+ S.D) [range]**	**Current diagnoses**						**Number of Diagnoses (% of total sample)**							
MIND-Set	236/309	99 F (41.9%)	37.1±13.27 [20-74]	150 Mood Disorder 71 Attention deficit hyperactivity disorder (ADHD) 55 Autism spectrum disorder (ASD) 22 Social Phobia 14 Panic Disorder 12 Generalised Anxiety Disorder 7 Anxiety disorder NOS* 6 Obsessive Compulsive Disorder 5 Post Traumatic Stress Disorder 4 Specific Phobia 2 Agoraphobia						**1:** 66 (27.9%) **2:** 65 (27.5%) **3:** 39 (16.5%) **>3:** 8 (3.38%)							

Note: Underline indicates that this parameter was input as a variable in the normative models. *NOS (Not otherwise specified).

Results:

Group level comparisons show consistent effects across cohorts: Group level maps for the faces>shapes (Fig1a) and faces>baseline (Fig1b) contrasts replicated prior literature. Overall, positive task effects (activations) for faces>shapes were found in: the bilateral inferior and middle occipital lobe and the calcarine cortex (V1) extending anterior-ventrally to the bilateral lingual and fusiform gyrus, and anterior-dorsally to the middle and inferior temporal gyrus; the bilateral amygdala extending into the hippocampus; the bilateral temporal pole; a dorsal region of the vmPFC; and the bilateral middle and inferior frontal gyrus. Overall, task-related deactivations were found across regions comprising the default mode network, including the anterior and posterior cingulate cortex and precuneus, the precentral gyrus and supplementary motor area and the inferior temporal lobe.

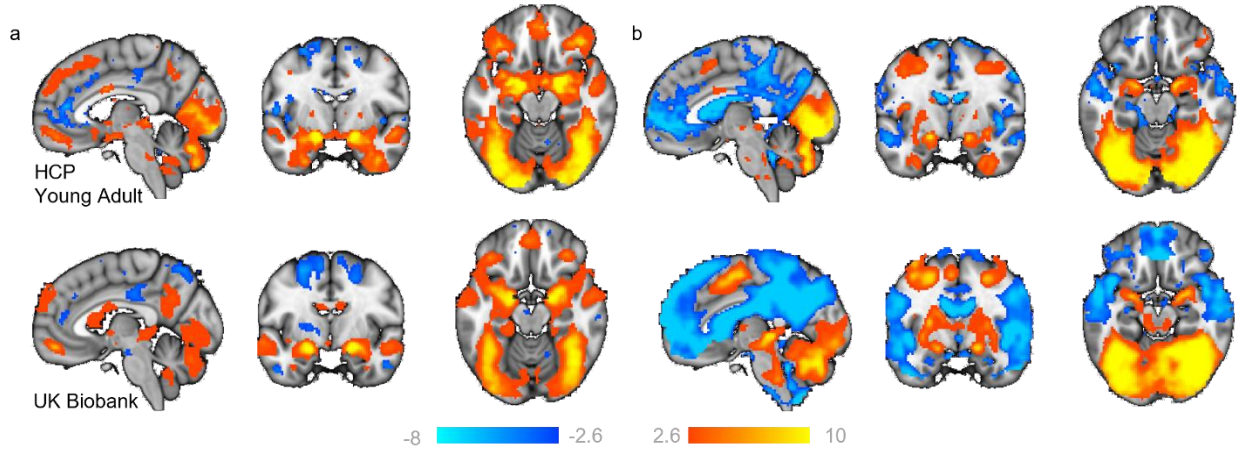

Figure 1: Task evoked activation. Two representative groups maps (from HCP Young Adult and UK Biobank), illustrating regions where participants show greater BOLD signal (z-statistic maps, thresholded at>±2.6) to (a) faces, as compare to shapes (faces>shapes), and (b) faces, as compared to baseline (faces>baseline). x,y,z = -4,-6,-16.

Fit of reference normative models: Normative models of EFMT-related BOLD activation were estimated for each voxel, for both the faces>shapes and the faces>baseline contrasts. Explained variance (EV) was good, especially in regions that showed activation at the group level (Fig 1) including the occipital lobe/visual cortex and the bilateral amygdala (faces>shapes: Fig 2a; faces>baseline: Fig 2d). As shown in Supplementary Figure 2a and 2c in most voxels the skew and kurtosis was acceptable. For a very small proportion of voxels this was not the case; the most ventral region of the vmPFC (i.e. the bottom border of the brain) was the most negatively skewed which we interpret to reflect the varying degrees of signal dropout, more so than biological variation. The few voxels with positive kurtosis were spatially overlapping with regions that were negatively skewed, which likely reflects the extended negative tails of the distributions in these voxels. To summarise, most models had good explained variance, and skew and kurtosis around 0.

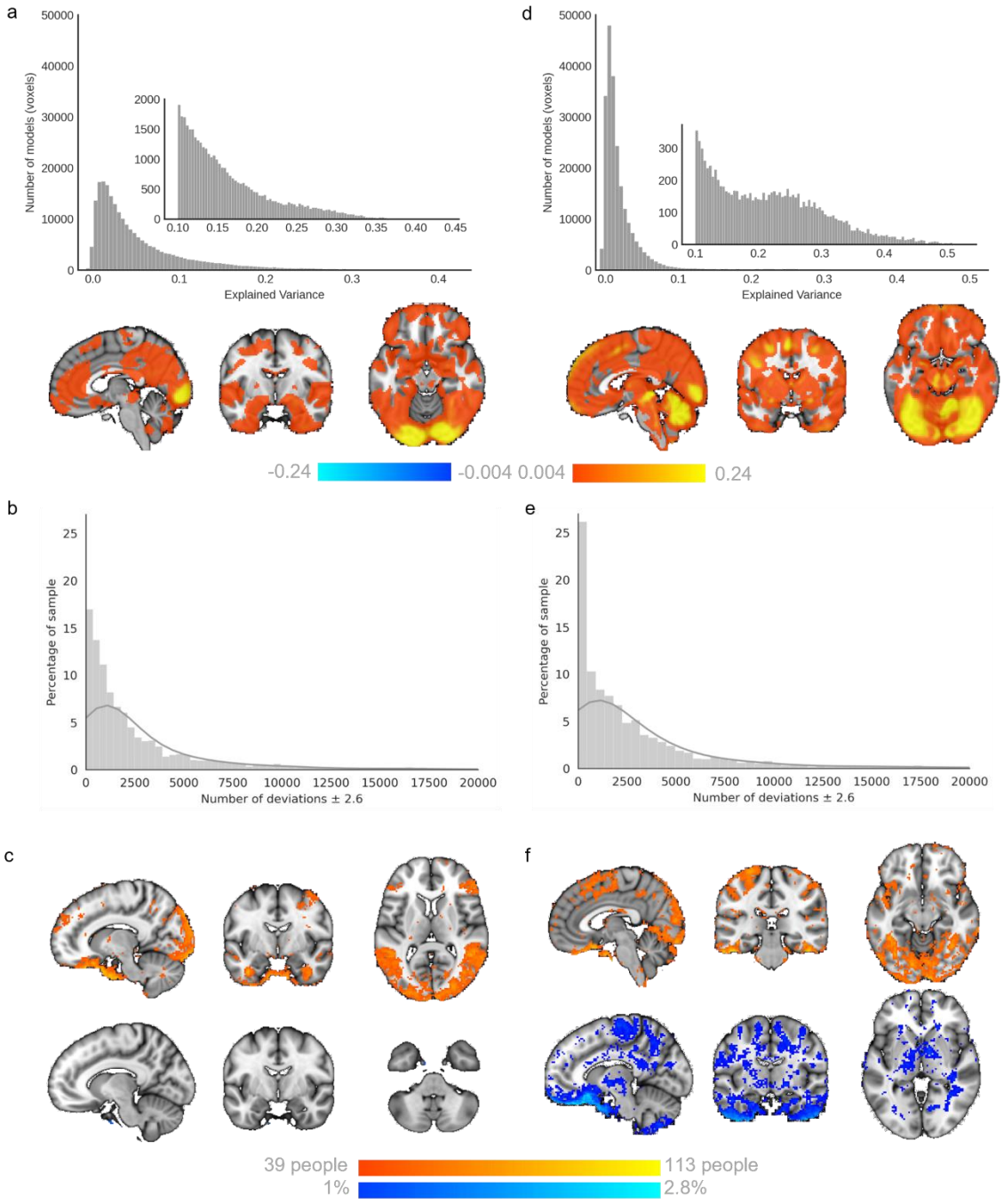

Figure 2: Evaluation and deviation scores from the faces>shapes (left) and faces>baseline (right) normative models. Explained variance is high in the normative models, irrespective of whether they are built using the face>shapes contrast (a), or the faces>baseline contrast (d). Histograms show the relative frequency of the total number of deviations that a participant has for each model (b,e). Normative Probability Maps illustrate the percentage of participants of the total sample who had positive (hot colours) or negative deviations (cool colours) > ±2.6 within each voxel, for the faces > shapes (c) and faces>baseline (f) models.

Voxel-wise deviations show considerable inter-individual variability, especially within the task-network: For each participant we created a thresholded NPM (deviation scores > ±2.6), illustrating the voxels where that participant had greater or less activation than would be expected. Figures 2b and 2e show the frequency of the total number of deviations that individuals had from the faces>shapes, and faces>baseline models, respectively. Within each voxel, we then counted how many participants had positive or negative deviations (> ±2.6). The resulting brain maps illustrate the variability in the magnitude of functional activation per voxel, across the population for the two task contrasts (Fig 2c + f). This shows that: (i) there is considerable inter-individual variability underlying the mean effects and (ii) that the spatial distribution of individual deviations mostly occurs within the task network. Every voxel of the brain had at least one subject with a deviation > ±2.6 (not shown), although, as illustrated, there were regions including the medial occipital lobe extending to the bilateral fusiform gyrus and inferior temporal lobe, the bilateral inferior frontal gyrus extending to the precentral gyrus, and the posterior region of the vmPFC, wherein deviations were more frequently observed. As there was minimal differences in the evaluation metrics between models built using either contrast, and as the contrast faces>shapes is most commonly reported in prior literature, we use this as our primary contrast for our further analysis of the reference model.

Separable effects of input variables on model predictions: As shown in Figure 3, the direction of the relationship between input variables and the predicted BOLD activation, and the fraction of the explained variability can be meaningfully separated for interpretation. Some input variables, namely acquisition parameters, showed overlapping effects (with sensical direction flips) likely due to their relatively high correlation and limited variability across sites. For example, the number of target blocks, volumes acquired (not shown), use of multiband sequence (not shown), and the length of the TR (not shown) all showed a similar relation to predicted activity.

Increased age was related to decreased predicted activity across the peripheral/surface of the brain, as well as regions surrounding the ventricles, and increased activity in midline regions of the default mode network, the bilateral insula, the fusiform face area extending to the para-hippocampal gyrus and the superior temporal gyrus. Predictions were only minimally influenced by sex, and the spatial mapping of this relationship was broadly overlapping with that of intra-cranial volume (not shown).

We further illustrate the ability of this method to disentangle the influence of task design choices, on predicted activation. For example, the influence of the matching rule and the stimuli presented. Being told to match the emotional expression, as compared to matching the faces, related to increased predicted BOLD activity within subcortical areas including the bilateral putamen, caudate body and medio-dorsal thalamus. Attending to the emotional expression also predicted increased activity within the superior frontal gyrus extending to the supplementary motor area, the posterior medial temporal gyrus the inferior temporal gyrus, and the medial temporal pole. Conversely, when participants were asked to match faces, the model predicted greater activation within the bilateral fusiform gyrus, the middle temporal gyrus, the superior temporal pole, the dorsolateral prefrontal cortex, and a large area of the inferior parietal gyrus extending to

the supramarginal and angular gyrus. Additionally, when stimuli from the Ekman series were used the model predicted greater activation within the bilateral inferior occipital gyrus and the calcarine cortex (V1), the bilateral lingual and fusiform gyrus extending to the inferior temporal gyrus, as well as in the medial cingulate cortex, an anterior region of the vmPFC, the superior medial prefrontal cortex, and subcortical regions including the ventral posterior thalamus, the posterior putamen, para-hippocampus, hippocampus and amygdala. Conversely, the use of the Nim-Stim Set stimuli related to greater activity within default mode regions, including a large area of the ventromedial/medial prefrontal cortex, precuneus, cuneus, as well as the supramarginal gyrus which extended medially to the anterior and posterior insula, which in turn extended laterally to the superior and medial temporal gyri.

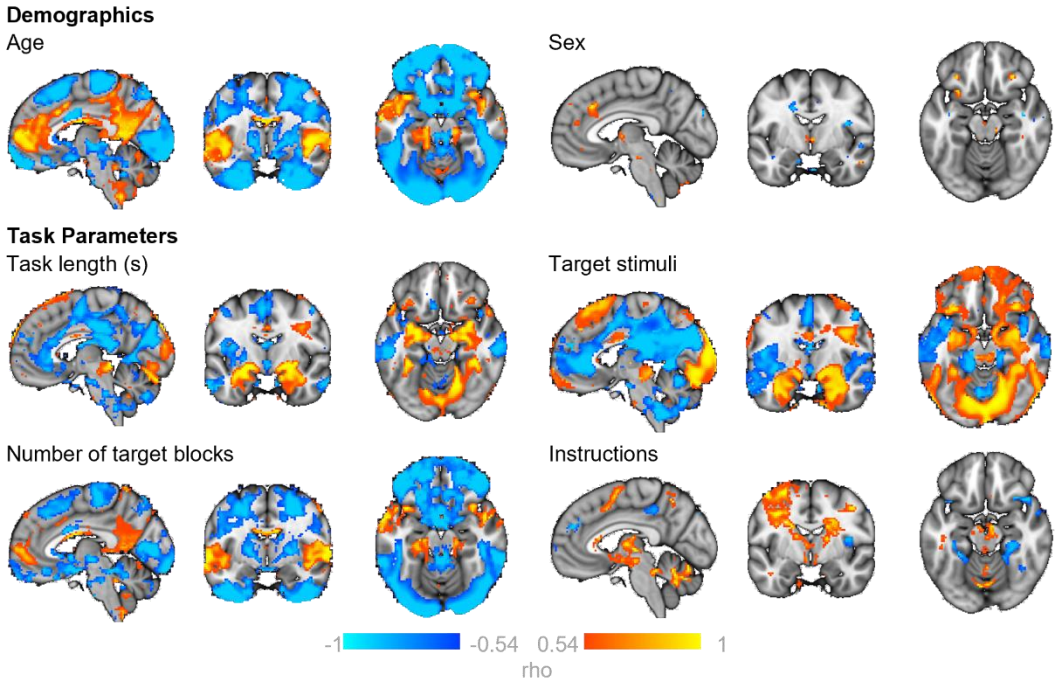

Figure 3: The relationship between input variables and the predicted BOLD activation for faces>shapes. Maps show the correlation coefficients (rho) thresholded by their respective coefficients of determination (rho^2>0.3) of selected model input variables. This can be interpreted as showing how predicted BOLD activation for the faces>shapes contrast relates to the input variables of the normative models. Positive correlations (warm colours) indicate greater activation for higher values of the input variable and negative correlations (cool colours) greater activation for lower values of the input variable (note that some variables are dummy coded, e.g. target stimuli, instructions) x,y,z = -4,-6,-16.

A traditional case-control comparison identifies very few differences between patients and controls: We performed a case-control comparison on the raw data, between the heterogeneous patient cohort, and the respective unaffected controls from the MIND-Set sample for faces>shapes and faces>baseline (Fig. 4). Few regions were identified as significantly different between the group for the faces>shapes contrast (Fig. 4a); patients had greater activation than controls in the left temporal medial

gyrus and bilateral posterior cingulate cortex, as well as in small regions of the supplementary motor area, and the genus of the anterior cingulate cortex. There were negligible differences between patients and controls for the faces>baseline contrast.

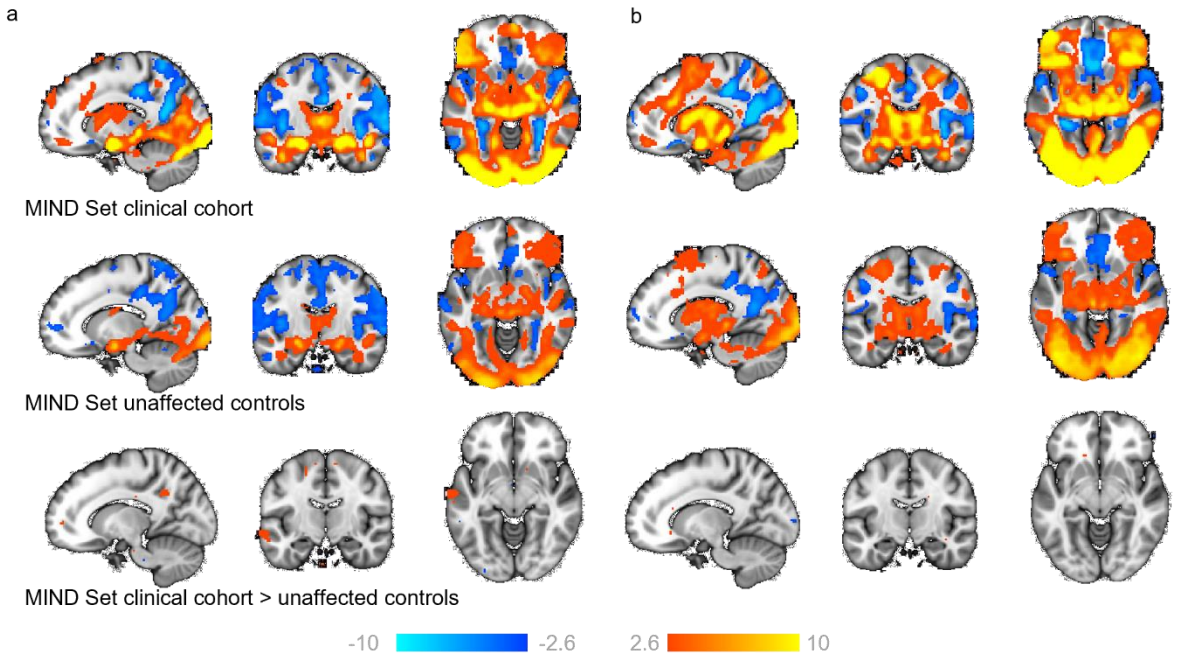

Figure 4: General linear model results comparing patients to controls for the faces>shapes and faces>baseline contrasts. Maps show regions activated (warm colours) and deactivated (cool colours) for faces>shapes (a) and faces>baseline (b), for patients (top row) and unaffected controls (middle row) from the MIND Set cohort. (c) Regions where patients have more activation than controls (bottom row) (z-statistic maps, thresholded at > ±2.6). x,y,z = -14, -13, -9.

Relating normative model deviations to psychopathology: As evidenced in Table 1 (see Diagnoses), the naturalistic MIND-Set sample has many patients with co-occurring and heterogenous mental health diagnosis, with or without neurodivergence, and is therefore representative of true clinical populations.

Fit of models to MIND-Set cohort: For faces>shapes and faces>baseline models, the explained variance of the clinical test data was quite low suggesting that the variance in BOLD signal was driven by individual differences, as opposed to the variables included in the model. The skew and kurtosis of the models were centred around zero. See Supplementary Figure 4a-f for histograms of these evaluation metrics, and their respective illustration on the brain.

Frequency of deviations differentiates patients from unaffected controls: We compared the frequency of extreme deviations, at the level of each individual, between patients from the MIND-Set cohort and unaffected controls from the reference cohort test set for each model type (faces>shapes: Fig5b,c; faces>baseline: Fig5e,f). MIND-Set patients had a greater frequency of deviations relative to the reference

cohort for the faces>shapes contrast (Mann-Whitney U test = 568662.5, p = 3.08x10^{-9} ; Fig5b). These deviations were most frequently identified in the medial prefrontal cortex and the bilateral medial and inferior temporal lobe (Fig 5a). In contrast, for the faces>baseline contrast individuals from the reference cohort had a greater frequency of deviations relative to MIND-Set patients (Mann-Whitney U test = 384906.0, p = 2.3x10$^{-5;}$ Fig 5 e). The spatial distribution of these deviations is, however, strongly localised within the vmPFC (Fig 5d) which is well-known to be problematic area for signal distortion artefacts in fMRI, therefore we do not interpret this difference as being biologically meaningful.

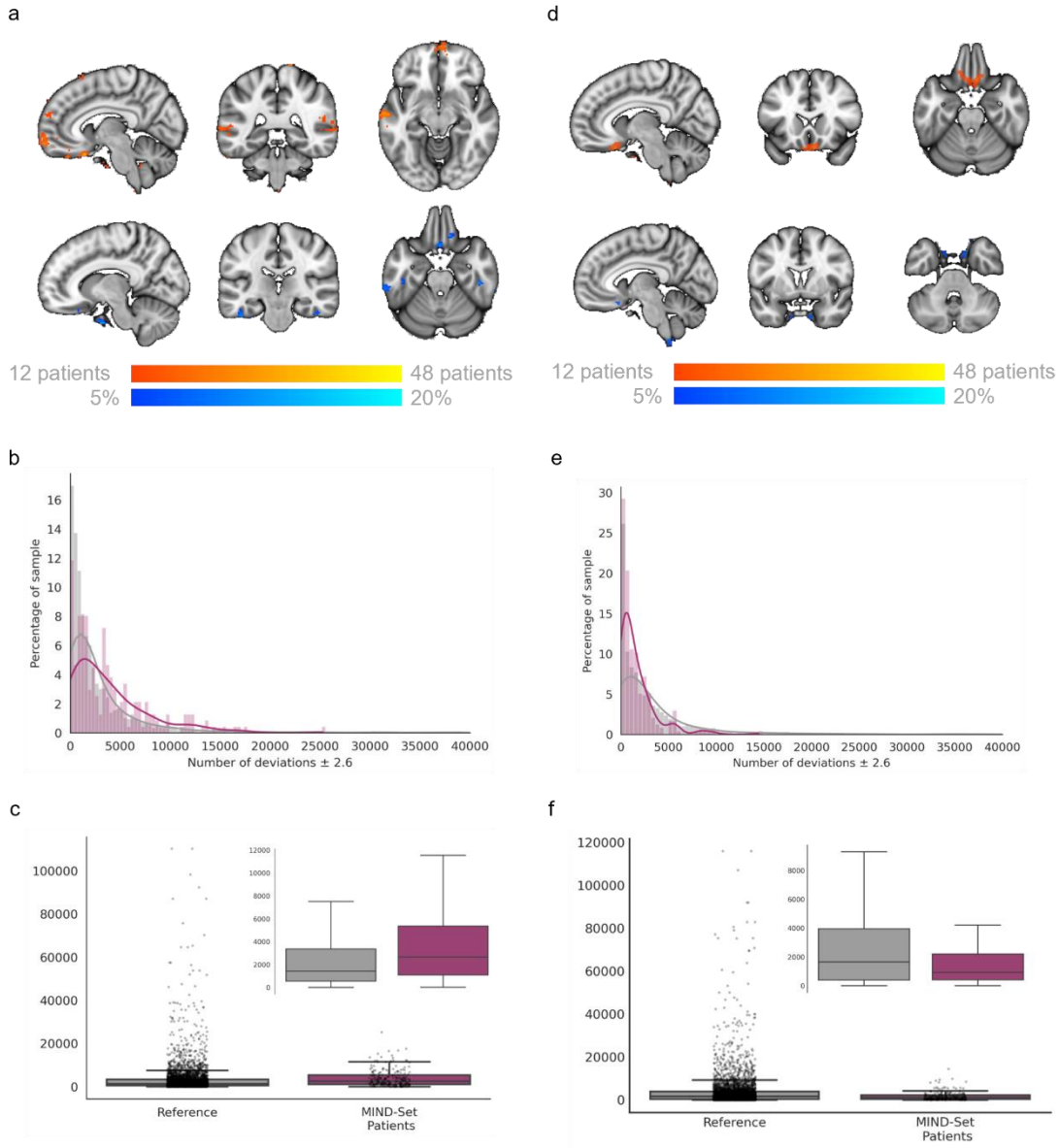

Figure 5: Testing the faces>shapes (left) and faces>baseline normative models with the MIND-Set cohort. Normative Probability Maps illustrate the percentage of participants of the clinical sample who had positive (hot colours) or negative deviations (cool colours) > ±2.6 within each voxel, for the faces > shapes (a) and faces>baseline (d) models. Histograms and box plots show the relative frequency and mean number of the total deviations that a participant has for faces > shapes (b,c) and faces>baseline (e,f) models.

Deviations from the reference normative models are associated with cross-diagnostic symptomatology: We measured the association between individualised patterns of deviation and cross-diagnostic symptom domains by inputting whole-brain (unthresholded) deviation maps and factor loadings for negative valence, cognitive function, social processes and arousal/inhibition domains to sparse canonical correlation analysis. Significant out of sample associations were detected both for faces>shapes and faces>baseline contrasts (mean r of test splits 0.224 and 0.151 respectively, both $p < 0.001$ by permutation test; Fig 6b, e) but with distinct patterns of effects both in terms of symptom domains and associated brain regions. More specifically, for the faces>shapes contrast, decreased functioning predominantly in the negative valence and arousal/inhibition domains (Fig 6a) was associated with a pattern of deviations including the bilateral insula, medial prefrontal cortex and pre- and post- central gyri, the bilateral inferior temporal gyrus, lingual gyrus, bilateral hippocampus and the right thalamus as well as the regions in the medial cerebellum (Fig 6c). By comparison, for the faces>baseline contrast factor loadings for cognitive functioning and arousal/inhibition (Fig. 6d) were most strongly related to a pattern comprising bilateral insula, the anterior-to-medial cingulate cortex, bilateral medial prefrontal cortex extending to the supplementary motor area, the pre- and post- central gyri, the bilateral superior frontal gyrus, and the bilateral hippocampus, caudate, putamen and amygdala (Fig 6f). The SCCA analysis was repeated to relate participant's diagnoses with their whole-brain (unthresholded) deviation maps. In contrast to the cross-diagnostic symptom domains, there was no association between diagnostic labels and deviation scores. Mean canonical correlations were small (mean r of test splits <0.09 for both faces>shapes and faces>baseline models), and this was not statistically significant as determined by 1000-fold permutation testing.

Spatial extent of deviations highlights similarities across, and differences between diagnoses: We were interested in the spatial distribution of the deviations within the clinical sample, and whether this varied according to the participant's mental health diagnosis or neurodivergence (note that subjects can be in multiple categories; Figure 7). Across disorders, patients frequently had positive deviations in regions including the left anterior medial temporal gyrus, and the bilateral posterior medial temporal gyrus, and the anterior region of the vmPFC. Conversely, negative deviations were common across diagnostic groups within the bilateral posterior inferior temporal gyrus, and the inferior occipital gyrus. There were some further commonalities across similar disorders, such as widespread deviations within the vmPFC in mood disorders and neurodivergence, and opposing changes within the dmPFC in social and generalised anxiety disorder. Additional unique regions of frequent deviations within disorders suggests that the spatial patterns of deviations may be related to disorder-specific changes in activation during the EFMT task. We were further interested to see whether the number of co-occurring diagnoses and/or neurodivergences influenced the spatial patterns of the deviations (Supplementary Figure 5).

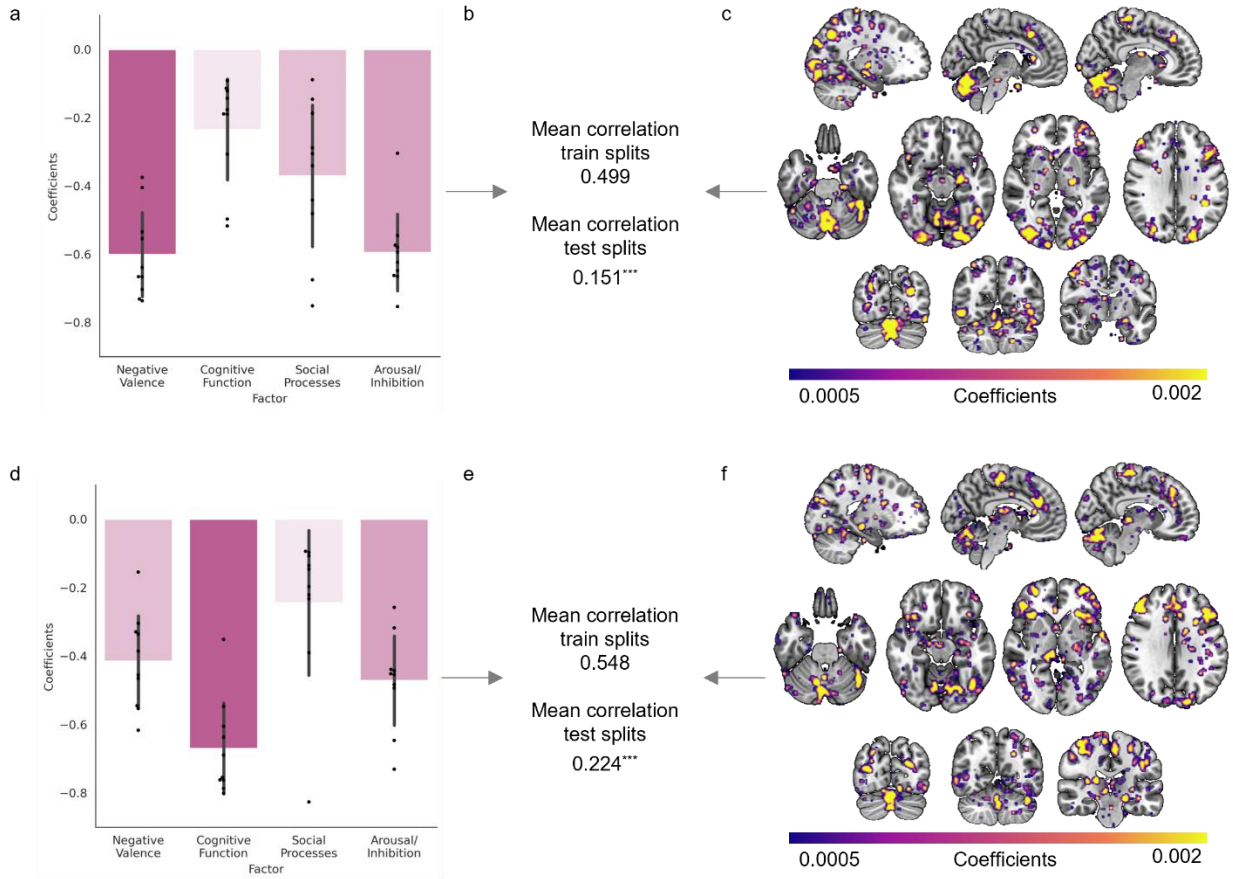

Figure 6: Sparse canonical correlation analyses (SCCA) between functional domains, and deviation scores from faces>shapes or faces>baseline normative models. Weights per factor to latent variable of psycho-social functioning (a,d). Canonical correlation for between 4 functional domains and whole-brain deviation scores from (b) faces>shapes and (e) faces>baseline normative models (regularisation 10%). Voxel-wise weights to latent variable of deviation scores from (c) faces>shapes normative models and from (f) faces>baseline. All results are statistically significant with 1000-fold permutation tests (*** = p<0.001).

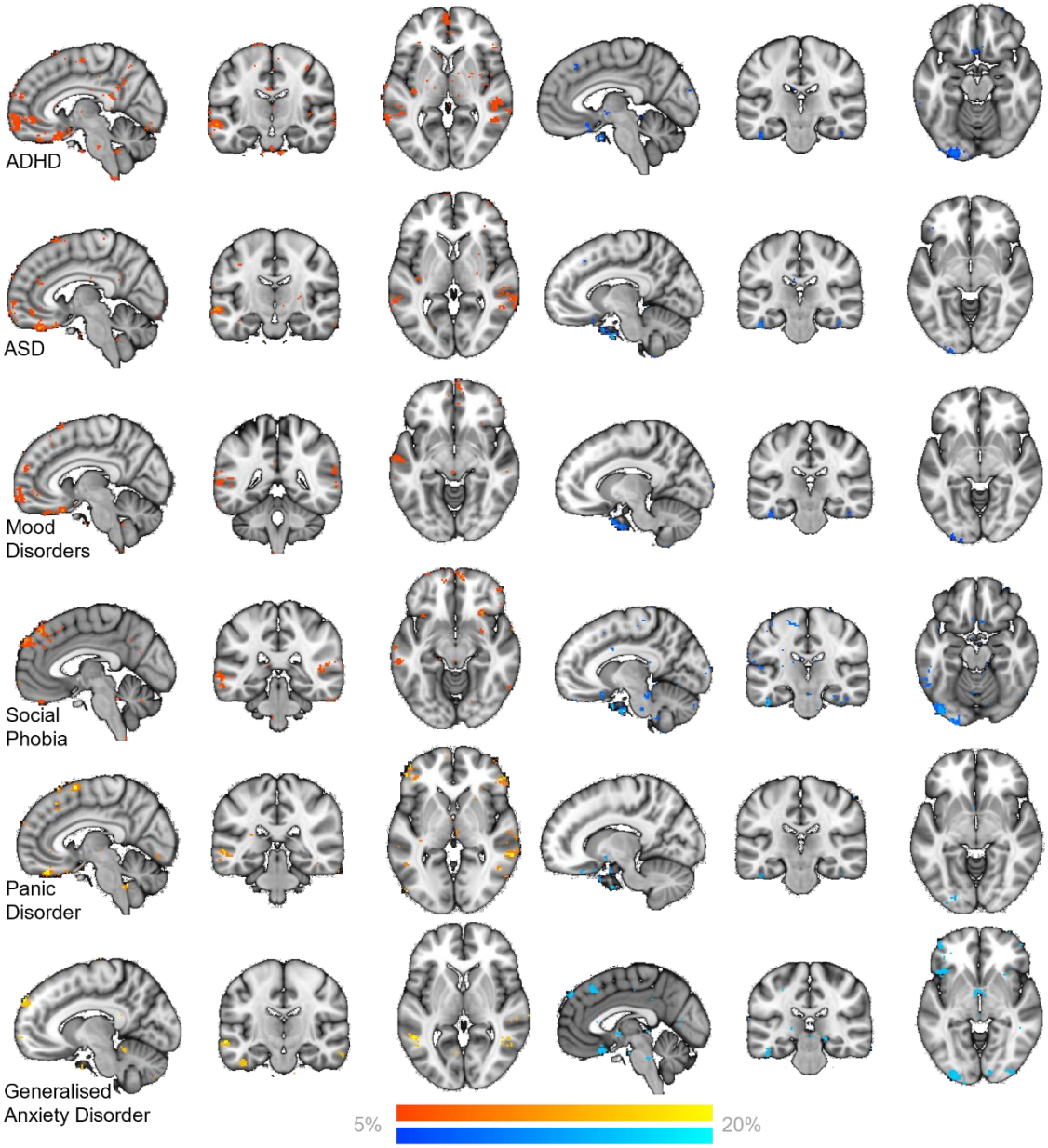

Figure 7: Heterogeneous location of deviations in predicted BOLD signal for different types of neurodivergence, and mental health diagnoses. Maps illustrate the percentage of participants with a neurodivergence or mental health condition who had positive (left; hot colours) or negative deviations (right; cool colours) > ±2.6 within each voxel [minimum = %5 of sample, or 1 participant where 5% was a participant count less than 1, maximum = 20% of sample size].

Discussion:

In this study we made use of six large publicly available datasets of participants completing the fMRI EFMT to build a reference normative model of functional activation underlying emotional face processing. We collated data from over 7500 participants and show that our voxel-wise models can explain up to 50% of variance in observed BOLD signal, with the remaining unexplained variance representative of individual differences in functional activation (deviation scores). We unpacked the variance explained by the models, to show how the predicted activation related to the models' input variables, namely demographics, variations in task design, and acquisition parameters. Lastly, we tested our reference model with data from a sample of patients with heterogenous and frequently co-occurring psychiatric conditions (affective and anxiety disorders, and neurodevelopmental conditions). Our analyses show that: (i) there is considerable inter-individual variation superimposed on the group effects customarily reported in fMRI studies, (ii) that such variation is predictive of psychiatric symptom domains in a cross-diagnostic fashion and (iii) while an overall effect of diagnosis was evident, this was highly individualised in that the overlap of deviations amongst individuals with the same diagnosis was low. This implies that there are brain regions wherein patients more frequently have deviations irrespective of the type of diagnoses, and other regions wherein the frequency of deviations appears specific to the mental-health condition or neurodivergent diagnosis.

A key feature of the normative modelling framework in the context of multi-site fMRI data is that it allows us to aggregate data across multiple samples by binding them to a common reference model. This provides multiple benefits: it removes site effects from the data without requiring the data to be harmonized[29], which avoids the introduction of certain biases due to harmonisation[30] and allows meaningful comparisons to be drawn across studies. For example, this allows aggregation of different studies to better understand variation across cohorts or across the lifespan and to understand the effect of different task parameters on functional activity across cohorts. Moreover, by placing each individual within the same reference model this provides the ability to quantify, compare and ultimately parse heterogeneity across studies.

Normative models can be used to uncover and explain functional heterogeneity in task-evoked activation: Traditional group-level task contrasts, as shown in Fig 1, inform us of the region's most consistently activated across participants/groups during task conditions. Their interpretation has relied heavily on the assumption of spatial homogeneity of activation between subjects; an assumption that the deviation scores from our reference model show to be largely untrue (Fig 2). We show that such group effects reflect a small proportion of the variation amongst individuals and using the normative modelling framework we map the underlying heterogeneity, separating variation in the intensity and spatial extent of task-evoked functional activation between-subjects attributable to known factors such as site effects, demographics, acquisition parameters, and differences in EFMT paradigm design. More importantly, we show that residual differences

in the neuronal effects elicited by the task are highly meaningful in that they were predictive of psychiatric symptomatology and can be used to understand inter-individual differences in functional anatomy and its relation to clinical variables. In our test reference population, while every voxel of the brain had at least one participant with a large deviation, some regions considered active during the faces condition (as compared to shapes), such as the medial occipital lobe, fusiform gyrus and inferior temporal lobe, were also regions in which positive deviations were frequently observed.

When building our reference models, we chose to include and control for multiple variables that we reasoned may influence the BOLD signal observed. These included demographic factors such as age and sex, and task design choices that could influence the BOLD signal generated, as well as acquisition parameters that could influence the BOLD signal recorded. Some effects, such as that of age and task instructions were relatively strong and interpretable, for example, increased age predicted decreased activity in surface areas of the brain and regions surrounding the ventricles likely reflecting decreased signal due to age-related atrophy, and instructing participants to match emotional expressions, as opposed to matching faces, increased the predicted activity in the thalamus which may reflect increased engagement of regions associated with affective processing. On the other hand, other variables explained relatively little variance in the predictions (e.g. sex). In our sample many predictor variables were collinear across sites which limited our ability to detect systematic differences resulting for example from differences in the task paradigm. In this work we decided to keep all variables in the model and used structure coefficients to identify the importance of different variables, which are relatively insensitive to collinearity. This follows prior work to identify specific effects of input variables on model predictions, for example the influence of specific adversity types on predicted morphometric changes (Holz et al., *in prep*). However future researchers may consider reducing the dimensionality of their inputs prior to model. Future studies with larger numbers of more diverse samples (e.g. more variations on the basic task design), as is possible in consortium such as ENIGMA, will allow for more fine grained analyses of the effect of task parameters on inter-individual variation within the population.

Deviations from the reference models are clinically meaningful and have relevance to cross-diagnostic symptomatology: We demonstrated that distinct patterns of deviations, derived from each model type (faces>shapes or faces>baseline), were associated with unique profiles of functioning across four transdiagnostic domains. The distinct patterns of effects, in terms of the implicated symptom domains and associated brain regions, make sense in the context of relevant existing literature. For example, negative affect, impulsivity and emotional liability have previously been related to functional activity within the bilateral insula, motor cortex and hippocampus[31], and cognitive functioning has been linked to activity within the medial prefrontal cortex, anterior-to-medial cingulate cortex, superior frontal gyrus. This not only validates the interpretability of findings from these normative modelling analyse, but also illustrates the potential for future researchers to use individualised deviation maps to better understand the neural

processes that underly cognitive and affective functioning, within and across diagnostic boundaries. Furthermore, approaching dysfunction through the normative modelling framework and transdiagnostic functional domains appears to more closely relate to underlying biology. This reflects practitioners implementation of clinical care and the use of overlapping treatments for differing disorders, which often does not fit a binary classification paradigm. Using this modelling approach may also better allow for the quantification of neurodivergence, not as being 'disordered' but rather as varying phenotypic expressions along a characterised spectrum.

It should be noted, however, that within any one voxel of the brain, only ~20% of the clinical sample (be that in the total sample, or within disorders) had large deviations. This suggests that the exact location of deviations is very variable between individuals, and likely explains why many prior studies have not found significant differences when performing traditional case-control analyses. In this study, we aimed to estimate the degree to which the deviations from the normative models were associated with cross-diagnostic symptomatology, but other approaches may also be useful, as outlined in Rutherford et. al. (2023). For example, clustering algorithms could be applied to derive a stratification of individuals[4, 5] or to identify heterogenous yet convergent functional processes (many-to-one functional mappings)[33], and supervised learning methods may be useful to assess the degree to which specific clinical variables can be predicted from the patterns of deviation we report.

Different task contrasts hold unique information about psychopathology: Interestingly, the normative models of functional activation built using the faces>shapes have a different pattern of association with symptomatology relative to the faces>baseline contrast. This suggests that the two contrasts carry complementary information about psychopathology. The frequency of deviation scores was significantly greater in the clinical cohort, compared to the reference cohort, when using the faces>shapes contrast, and the weights attributed to each of these deviations (at a voxel-level) in the SCCA were associated with different symptom domains. Neither contrast was significantly predictive of diagnosis. By comparison, the relationship between the frequency of deviation scores and domains of function was stronger when using models built using the faces>baseline contrast, which was further supported by the stronger canonical correlation between factor loadings for functional domains and deviations from the faces>baseline models. Taken together, this could be interpreted to suggest that widespread deviations, best captured by the faces>shapes contrast, are indicative of global alterations in functioning which are broadly linked to different clinical diagnoses. By comparison, fewer but more focal deviations and/or the ability to detect abnormal baselines of activation[34, 35], best revealed using the faces>baseline, have greater relation to specific functional domains. Future researchers should carefully consider the task contrast used to construct their normative models.

Limitations and future directions: Concerns for the within-subject reliability of task-based fMRI data[36] are not to be dismissed in the context of our models which are currently built on cross-sectional data. While we acknowledge the limitations imposed due to the limits of test-retest reliability of task fMRI, our results nevertheless provide encouraging evidence for the use of task fMRI readouts as individualised biomarkers as we show by their ability to predict clinical variables in the context of SCCA. While we were not able to assess test-retest reliability directly within the context of normative models due to a lack of test-retest data for the EFMT, one great strength of the normative modelling approach is the shift from looking only at mean activity, to estimating the underlying variance. This can implicitly down-weight regions or individuals that are less reliable. Indeed, it could be expected that repeated sampling would fall within the same variance distribution, and as such our broad understanding of brain function remains quite stable. The normative modelling framework is also ideally positioned to directly test the reproducibility of fMRI within subjects. In follow-on work to the present manuscript, we are currently developing an extension to explicitly include test-retest variability in the model by testing reference models with repeat scans from participants, and compare individuals' deviation scores between the two tests, whilst explicitly quantifying within subject variance, such that it provides a lower bound on the size of deviation that can be considered meaningful (Bučková et. al., *in prep*). Alternatively, where multiple repeats are available, hierarchical models can be used to accommodate dependencies between subjects[29] which would provide more precise estimates of individual deviations. The application of the normative modelling method to fMRI can easily be generalised to other tasks (e.g. the monetary incentive delay incentive processing task or n-back work memory task) and need not stop at predicting functional activation. With the right data sets, this method could use fMRI data to predict many other variables including psychophysiological responses or subjective ratings of affect.

With this work, we show the potential for the normative modelling framework to be applied to large task-based fMRI data sets to bind heterogeneous datasets to a common reference model and enable meaningful comparisons between them. Using this approach, we illustrate the heterogeneous intensity and spatial location of task-evoked activation within the general population[2] using the EFMT in a sample of over 7500 participants. Further, we applied this model to patients with a current diagnosis (affective and anxiety disorders, ASD and/or ADHD) and demonstrate the transdiagnostic clinical relevance and further potential for deviation scores derived from this method. The potential of this method is clear; normative modelling of task-based functional activation can facilitate a better understanding of individual differences in complex brain-behaviour relationships, and further our understanding of how these differences relate to mental health and neurodivergence.

Acknowledgements:

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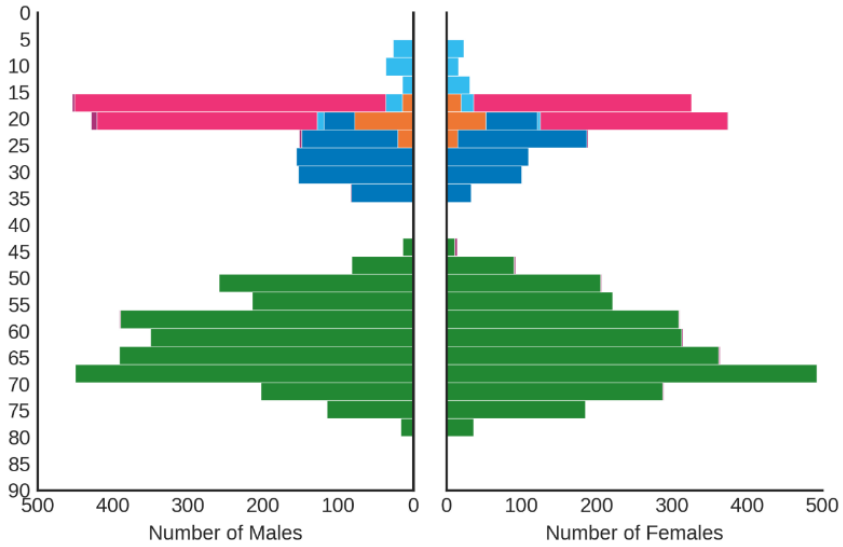
SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS – *Sample Details*:



Supplementary Figure 1: Age and sex distribution of the total reference population.

SUPPLEMENTARY METHODS – *Signal coverage of the prefrontal cortex (PFC)*:

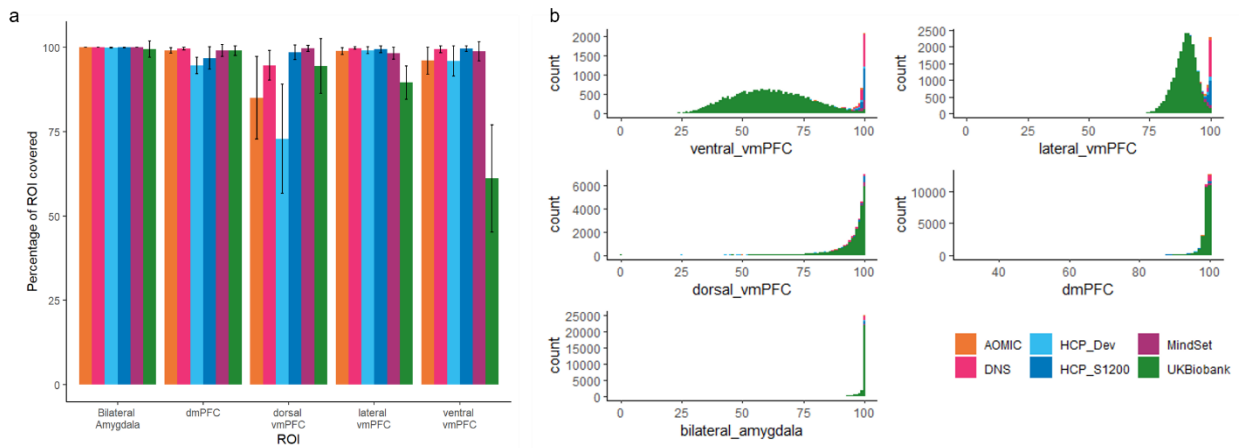
Due to air-tissue inhomogeneities which can diminish the acquired BOLD signal to such a degree that no activations are visible, a notorious effect within the ventral PFC, we performed targeted quality control for this extended region. Binary ROI masks were created for the dorsal ventro-medial PFC (d-vmPFC), ventral vmPFC (v-vmPFC), lateral vmPFC (l-vmPFC) and the dorso-medial PFC (dmPFC), as defined by the AAL2 atlas regions 25, 27, 33 and 1 respectively (see Supplementary Figure 1C). The percentage of voxels with an absolute value greater than 0 for the contrast faces > shapes within each ROI was determined (i.e. where any signal was present regardless of its relative direction; see Supplementary Figure 1A,B). While most sites had good coverage, the coverage within the ventral and lateral vmPFC regions were particularly variable for the UK Biobank data. We therefore performed this step *only on data from the UK Biobank site*; this selectivity was made possible by the large number of participants we had access to, and our need to include but a fraction of the total available sample. We ranked participants in descending order of the percent of their v-vmPFC, l-vmPFC, d-vmPFC, and dmPFC covered, respectively, and selected the first 5000 participants. We also collected the percentage covered value for a bilateral amygdala ROI mask, but made no exclusion/inclusions on this basis as coverage was very high across all participants and all sites.

Supplementary Table 1: Motion QC

Site	Full sample size	Included	Excluded
AOMIC	217	217	0
DNS	1263	1246	17
HCP Young Adult	1044	1044	0
HCP Development	256	256	0
UK Biobank	26167	5000	N/A
MIND-Set	393	389	4

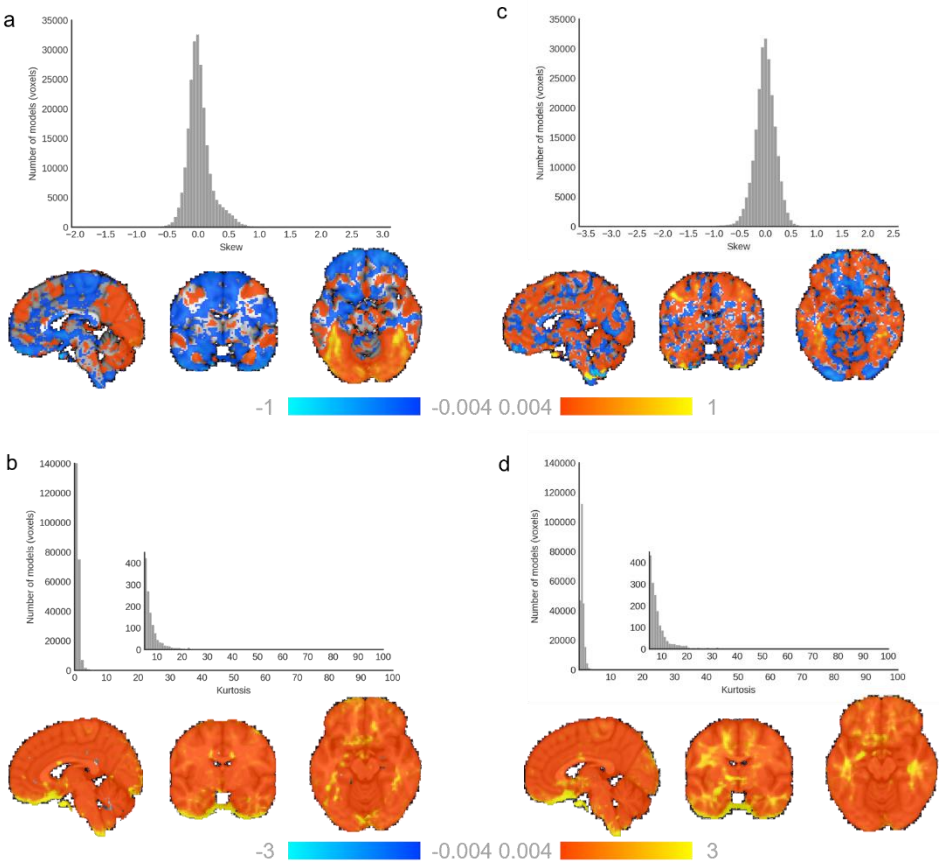
Supplementary Table 2: vmPFC QC

ROI	Site	Sample size (n)	Mean percentage of ROI covered	Standard deviation
Bilateral Amygdala	AOMIC	217	100	0
	DNS	1246	100	0
	HCP Development	256	99.94936	0.162845
	HCP Young Adult	1044	99.98188	0.098589
	MIND Set	389	99.99966	0.006707
	UK Biobank	26120	99.47363	2.399575
dmPFC	AOMIC	217	99.10345	0.830591
	DNS	1246	99.61285	0.411399
	HCP Development	256	94.6524	2.460686
	HCP Young Adult	1044	96.85686	3.318827
	MIND Set	389	99.069	1.785034
	UK Biobank	26120	99.0493	1.405906
Dorsal vmPFC	AOMIC	217	85.08059	12.23881
	DNS	1246	94.68589	4.406996
	HCP Development	256	72.90154	16.11571
	HCP Young Adult	1044	98.58104	2.192929
	MIND Set	389	99.75218	0.886996
	UK Biobank	26120	94.50698	8.107753
Lateral vmPFC	AOMIC	217	98.90096	1.063159
	DNS	1246	99.82392	0.33135
	HCP Development	256	99.14376	1.003451
	HCP Young Adult	1044	99.46709	0.978404
	MIND Set	389	98.23297	1.745961
	UK Biobank	26120	89.56122	4.919904
Ventral vmPFC	AOMIC	217	96.06479	3.960334
	DNS	1246	99.45099	0.964661
	HCP Development	256	95.999	4.42593
	HCP Young Adult	1044	99.63665	0.85699
	MIND Set	389	98.83508	2.868568
	UK Biobank	26120	61.17452	15.9091



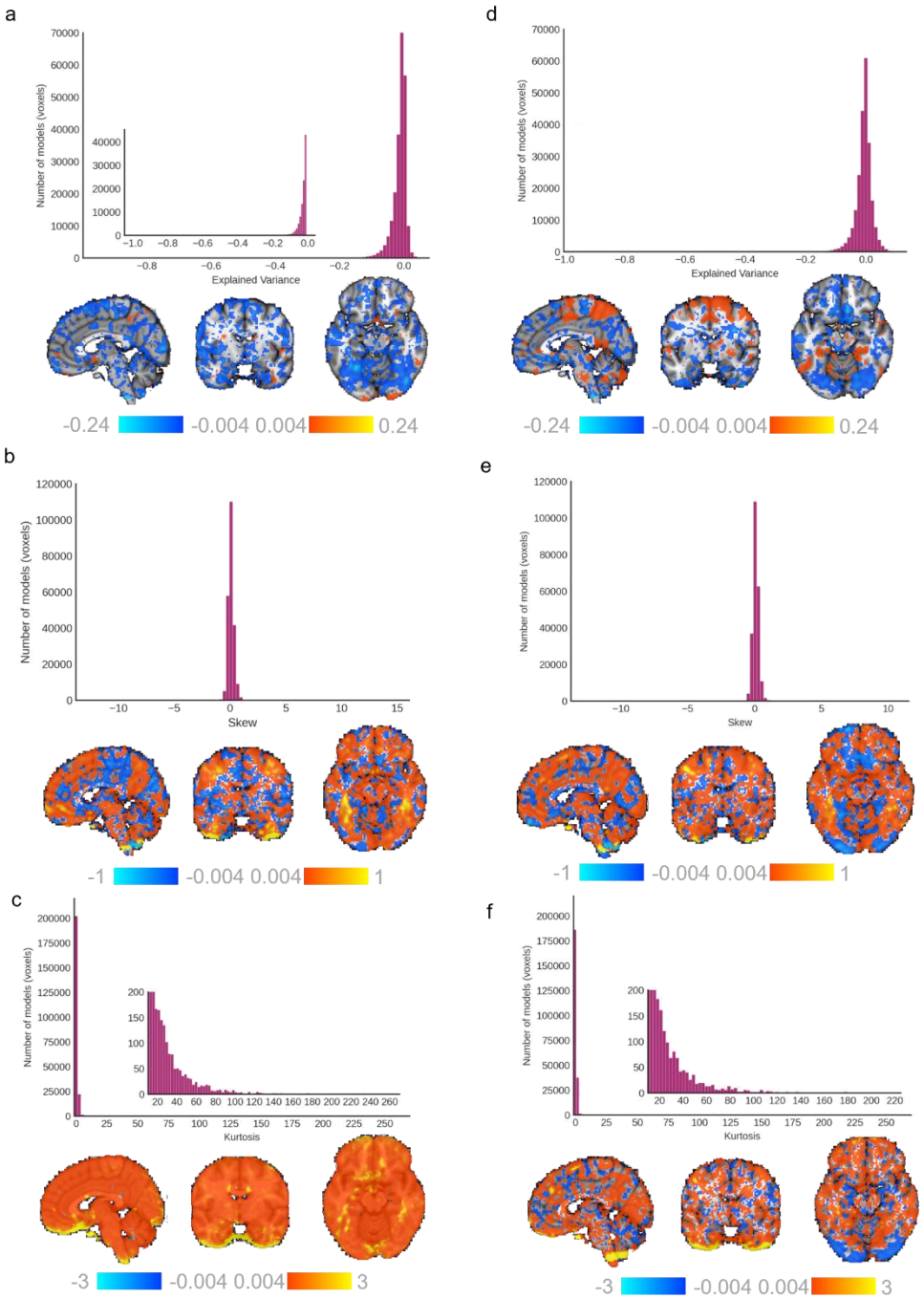
Supplementary Figure 2: vmPFC QC metrics. (a) Mean percentage of each ROI with signal greater than 0, used for quality control. Error bars show +/- standard deviation (b) Stacked histograms (raw participant count) of the percentage of each ROI covered, coloured by site.

SUPPLEMENTARY RESULTS – *Evaluation of reference normative models*:



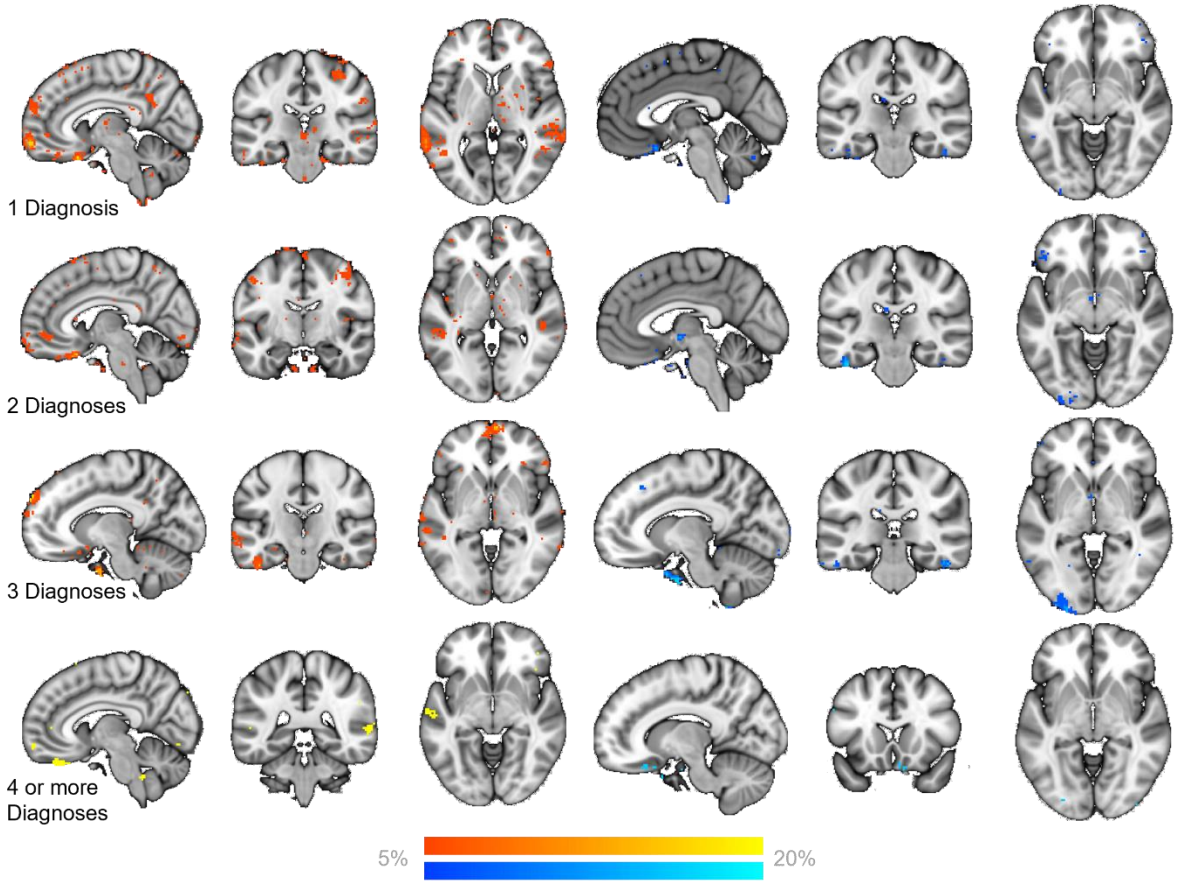
Supplementary Figure 3: Evaluation of the faces>shapes (left) and faces>baseline (right) reference normative models. Histograms show the skew (a,c), and kurtosis (b,d) of the normative models, and their respective illustration on the brain (x,y,z= 4,-6,-15).

SUPPLEMENTARY RESULTS – *Evaluation of normative models when applied to MIND-Set cohort*:



Supplementary Figure 4: Evaluation of the faces>shapes (left) and faces>baseline normative models when applied to MIND-Set cohort. Histograms show the explained variance (a,d), skew (b,e), and kurtosis (c,f) of the clinical data, as tested on reference normative models of EFMT related BOLD activation, and their respective illustration on the brain (x,y,z= 4,-6,-15).

SUPPLEMENTARY RESULTS – ***Location of deviations for increasing levels of co-occurring diagnoses:***



Supplementary Figure 5: Heterogeneous location of deviations in predicted BOLD signal for increasing levels of co-occurring diagnoses. Maps illustrate the percentage of participants with a neurodivergence or mental health condition who had positive (left; hot colours) or negative deviations (right; cool colours) > ±2.6 within each voxel [minimum = %5 of sample, or 1 participant where 5% was a participant count less than 1, maximum = 20% of sample size].

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