Amygdala responses to negative faces are not associated with depressive symptoms: cross-sectional data from 28 638 individuals in the UK Biobank cohort

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Introduction

Neurocognitive models of depression emphasise the role of amygdala in dysfunctional emotional processing (1,2). Specifically, increased amygdala responsiveness to negative stimuli is posited as a mechanism underlying the aberrant low-level emotional processing in depressed individuals, manifesting as a negativity bias in the perception and recognition of emotional stimuli (3).

Early brain imaging studies supported the view that patients with depression show larger amygdala responses to negative faces compared to controls (4–7); and a PubMed search (2021-04-05) for “amygdala AND depression” yielded > 4,000 hits, supporting the significance that this brain region has been assigned in the context of depressive disorder. Four recent meta-analyses (N = 2,383 for the largest by Li et al. 2020) also found increased amygdala activity during emotional tasks (including, but not limited to, facial stimuli) in depressed patients versus controls (8–11). Moreover, meta-analyses across psychiatric disorders suggest that amygdala hyperactivation is transdiagnostic, most pronounced in non-psychotic illnesses (e.g. anxiety

and depression) (12,13). Amygdala reactivity to emotional (facial) stimuli is often used in studies investigating antidepressant treatment effects (14) and depression risk (15,16), and is sometimes referred to as a *biomarker* for depression (17,18). In summary, various lines of research support the view that depression is associated with amygdala responses and, vice versa, amygdala responses are associated with depression, and risk of depression. While most previous studies compared clinical cases of depression to controls, it would be reasonable to expect such findings to translate to depressive symptoms in the general population, particularly considering the transdiagnostic nature of the association (12,13).

In this letter, we report on the largest study to date to test the association between amygdala reactivity and depressive symptoms based on UK Biobank (UKB) data. For transparency, we initially set out to investigate the association between sleep disruption and depression in UKB, focussing on amygdala reactivity as a key candidate mechanism linking the two associated variables (the details of our pre-registered study can be found at https://osf.io/xcv39/). When completing our pre-defined analyses, we found no association between the proposed mediator (amygdala reactivity) and our key outcome (depressive symptoms). We judge this unexpected finding to be sufficiently important for the field to merit a standalone report.

Method

The present study used cross-sectional data from the UKB cohort (19), which includes adults from the UK general population, recruited between 2006 and 2010. The target age range at recruitment was 40 to 69 years and no other exclusion criteria were applied. Participation rate was approximately 5%. Three in-person follow-up visits have been performed in subsets of the participants. Here we report on data from the first imaging visit, initiated in 2014. The NHS National Research Ethics Service approved all procedures (Ref. 11/NW/0382) and all participants gave written informed consent. Data were downloaded from the Biobank in May 2020.

Participants

Inclusion criteria were the same as for the UKB (19). We excluded participants if they reported a neurological condition (neurodegenerative disease, stroke, head injury or epilepsy), if consent was withdrawn or if data were missing for the outcome, predictor, or any of the covariates. The total number of participants included in analyses was 28,638.

Imaging protocol and study variables

Details of the magnetic resonance imaging (MRI) acquisition protocol, image processing pipeline, and image data files from the UKB have been previously described (20).

The dependent variable of interest was amygdala responses to faces > shapes from the so-called Hariri task (20–22). During functional MRI (fMRI), participants had to match one of two simultaneously presented images of negative emotional stimuli (angry and fearful facial expressions) with an identical target image (experimental block), or alternatively match geometric shapes (control block). An in-depth description of the imaging data processing can be found at https://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=1977. The 'Median BOLD effect (in group-defined amygdala activation mask) for faces-shapes contrast' (item 25052) served as dependent variable in our analysis. This variable is derived through extracting the median BOLD effect for the faces > shapes contrast from a group-defined region of interest (ROI) - the intersection of the original group-average ROI for this contrast, and an amygdala mask derived from the Harvard-Oxford structural atlas. The ROI is shown in supplementary figure 1.

Current depressive symptoms were measured on the day of imaging with the following four questions: "Over the past two weeks, how often have you… …felt down, depressed or hopeless?" (item 2050), "…had little interest or pleasure in doing things?" (item 2060), "…felt tired or had little energy?" (item 2080) and "… felt tense, fidgety or restless?" (item 2070). The response alternatives for the questions included 'Not at all', 'Several days', 'More than half the days' and 'Nearly every day', coded from 0-3. Hence, the total score (here denoted *depression score*) ranged from 0-12. The first three questions match core items from the validated Patient Health Questionnaire (PHQ)-9 (23), while the fourth question is similar to items from the anxiety measure GAD-7 (24). The measure has been used in previous studies of current depressive symptoms in the UKB cohort (25). Alternative item responses such as 'I do not know' or 'Prefer not no answer' were considered missing values. McDonald's omega for the depression score in the current sample was 0.79.

The following covariates were used in analyses: ***Age*** at assessment (item 21003), treated as a continuous variable, ***Sex*** (item 31), ***Education*** (item 6138), dichotomised into the categories "college/university degree" vs. "no college/university degree, ***Townsend deprivation index at recruitment*** (item 189), and ***Body Mass Index (BMI,*** item 21001) as a continuous variable.

Statistical analyses

Data were analysed with linear regression. In a first model, we investigated the crude association between depressive symptoms and amygdala responses. In the second model (considered our primary analysis) the following covariates were added: age, sex, education, Townsend deprivation index, BMI. Additional analyses were conducted with only the mood and anhedonia depression items (first 2 questions analogous with the PHQ-2 (26)). Because of the zero-inflated/skewed data for the main predictor (low depression scores in the sample) we also performed the following sensitivity analyses: 1) we removed all participants with depression score = 0 and repeated the same aforementioned analyses; and 2) we compared participants with depression score = 12 with those scoring 0, as well as participants with depression score > 6 compared to participants scoring 0, using independent sample t-tests. To explore possible age effects, we stratified the main analysis by age (≤ vs. > median), and investigated the interaction between below/above median age and depression score as a predictor of amygdala responses (suppl. table 10). We also performed follow-up analyses using self-reported depression diagnosis, as well as use of antidepressant medication and a lifetime depression diagnosis based on a mental health follow up in a subset of patients in 2017, see supplement, and an analysis looking at predictors of depression score, including the aforementioned covariates, as well as amygdala responses, to capture the potential bidirectional association (suppl. table 10). Furthermore, we performed a sensitivity analysis excluding 170 participants with a potential signal dropout within the amygdala mask (suppl. table 11) and ~~Lastly~~lastly, to quantify the evidence in favour of the null hypothesis (i.e. no association between depression score and amygdala responses), we present the data using Bayesian methodology (suppl. figure 3). Analyses were performed in R (27) with the lme4 package (28) and ggplot2 (29) was used for illustration. All analysis scripts can be found at: doi.org/10.5281/zenodo.5126666.

Results

The sample included 28638 participants (53% female) with a median (range) age 64 (44-82) years, mean (SD) BMI 26.4 (4.3) kg/m² and 52 % having attended college. Depression scores ranged from 0 to 12; median (IQR): 0 (0-2). Lower age, female sex, higher Townsend deprivation index, lower education and higher BMI were all significant predictors of higher depression scores (suppl. table 10). 1744 participants used antidepressant medication (as classified as Anatomical Therapeutic Chemical Classification System (ATC) code N06).

In the unadjusted model, depressive symptoms were not associated with amygdala responses (β (se): 0.0006 (0.0004), *p*=0.1206; figure 1A, table 1), however, lower age, male sex, college education and higher BMI all showed significant associations (figure 1B-F, table 1).

In the covariate-adjusted model, there was no evidence of a relationship between depressive symptoms and amygdala responses (β (se): -0.0001 (0.0004), *p*=0.7891; table 1). The results were consistent across younger/older participants (suppl. tables 6-8).

All sensitivity analyses as well as analyses involving only the two core depression symptom items showed consistent null-effects (results available in supplement) and the Bayesian model indicated strong evidence in favour of the null hypothesis (suppl. fig. 3).

Discussion

Our analyses show that amygdala responses to angry and fearful faces are not associated with depressive symptoms in 28,638 individuals from the UKB Cohort. The results stand in contrast to most previous studies, including four recent meta-analyses (8–11); although we note consistency with three other meta-analyses (30–32) that 1) similarly failed to observe an association and 2) found marked between-study heterogeneity in task design, facial expression (combinations of sad/angry/fearful), instructions (labelling emotion, matching faces etc), and analysis pipelines (33). In light of these inconsistencies, our data do not preclude the possibility that amygdala differences are present *in general* (i.e. for *all types* of tasks) between depressed patients and controls, or that other methods may reveal differences in brain structure, activity or connectivity. It is possible that altered perception of negative facial expressions might be an important feature of depression (34), but in light of the present data, it seems highly unlikely that amygdala responses to negative faces are of fundamental importance for the pathophysiology or symptomatology of depression.

The present study has a few limitations. The sample consisted of older, relatively healthy participants with generally low depression scores. Since most previous work has been conducted in younger samples, and taking into account the age effect seen in our analysis, we cannot exclude the possibility that amygdala reactivity to negative facial expression might be related to depression in younger people, or that depressive symptoms in older adults might be etiologically or qualitatively different in some way (35). However, exploratory stratified analyses showed no indications of such an effect. It has also been suggested that amygdala

function might decline over the lifespan (36,37) (albeit to a lesser extent than for many other brain regions) (38), which could potentially mask an effect in the current sample. Furthermore, depressive symptoms were assessed with only a subset of the questions from the validated PHQ questionnaire, and depressive symptoms might not be comparable to the case control studies included in the previously mentioned meta-analyses. However, it is important to note that additional supplementary analyses using other prior indicators of risk for depression (e.g. lifetime diagnosis of major depressive disorder) showed consistent null effects. Therefore, our findings imply that a potential effect of depressive symptoms on amygdala reactivity to negative faces in nonclinical samples might not be reliably present, or at the very least is smaller than previously thought (we observed a partial f2 of 0.000002 in the adjusted analysis), but as noted above caution should be exercised when extrapolating from our findings to clinical samples.

The fMRI task lasted only 5 minutes, without any behavioural outcomes. The amygdala is also treated as a single entity in the analyses, which does not take into account the region's functionally and anatomically heterogeneous collection of nuclei. Furthermore, since the UKB does not provide amygdala-specific data for individual task conditions, we cannot exclude the possibility that the result is due to the specific contrast (i.e. the comparison with shapes). However, task results point to an overall amygdala effect for faces compared to shapes as indicated by a positive intercept in the models – supporting task validity. Finally, a broader methodological reflection - relevant to the entire field of task-related fMRI - relates to growing evidence of low within-subject task reliability (39) and challenges of using regional brain activity for the study of individual differences (40).

Our study has several strengths. Importantly, our sample size is markedly larger than any other previous meta-analysis of the topic – indeed by a factor of 10 - and the standardised imaging protocol in UKB, including analysis pipeline, overcomes several methodological issues that may impact reproducibility in neuroimaging research (41).

Conclusion

We conclude that amygdala responses to negative emotional facial stimuli are not associated with depressive symptoms in a middle-aged/older population-based sample. While clinical cases of depression might be qualitatively different from depressive symptoms in the general population, an association between depression and amygdala responses to negative faces is not

likely to be as large as previously suggested. Our analyses suggest that amygdala responses to negative facial expressions should not be considered an important feature/biomarker of depressive symptoms, at least not in the general population.

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Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	**se**	***p-value***	**β-coefficient**	**se**	***p-value***
Depression score	0.0006	0.0004	0.1206	-0.0001	0.0004	0.7891
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0080	0.0013	< 0.0001	0.0089	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0005	0.0003	0.0700
Attended college	0.0091	0.0013	< 0.0001	0.0083	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0004	0.0002	0.0046

Table 1. Strength of univariable and multivariable-adjusted relationships in linear regression between depression score and amygdala responses to adverse emotional facial stimuli in UK Biobank participants. In the multivariable-adjusted model all predictors were forced in the model

Figure 1. Relationships of depression score (a) and other individual predictors (b-e) with amygdala responses. Dots represent individual data points and lines represent regression lines for continuous predictors and mean values for each group for dichotomous predictors.