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Neural activation of anxiety and depression in children and young people: A systematic meta-analysis of fMRI studies

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ABSTRACT

Functional magnetic resonance imaging (fMRI) studies consistently demonstrate altered neural activation in youth experiencing anxiety and depression in a way that is distinct from adult-onset disorders. However, there is a paucity of research systematically reviewing this, and no meta-analyses have been conducted using Activation Likelihood Estimation (ALE). The present study conducted a systematic literature search to identify fMRI studies in youth (age 4–18) with depression or anxiety disorders. 48 studies with over 2000 participants were identified that met the inclusion criteria. Significant foci were extracted. Five ALE meta-analyses were conducted: a) activation for both anxiety disorders and depression; b) activation for anxiety disorders only; c) activation for depression only; d) deactivation for both anxiety disorders and depression; e) deactivation for depression. Results indicated significant clusters of increased activation in the bilateral amygdala for youth with internalising disorders, and specifically for those with anxiety disorders. Significant increased activation extended into the dorsal anterior cingulate, entorhinal cortex, the putamen, and the medial and lateral globus pallidus in youth with anxiety disorders. These findings help to detail the nature of anxiety being an amygdala hyperactivity disorder, whilst also defining the distinction between neural activation patterns in anxiety and depression.

1. Introduction

Internalising disorders such as depression and anxiety are becoming increasingly common, with 4.4% and 3.6% of the population worldwide receiving diagnoses in these areas respectively; this makes depression the single largest contributor to global disability, while anxiety is the sixth (World Health Organisation, 2017). The prevalence of disorders in children and young people (CYP) is of particular concern, with one in eight 5–19-year olds now reporting at least one mental health disorder (MHD) in the United Kingdom (NHS Digital, 2018). Specifically, while the rates of some types of disorders in CYP have remained broadly stable over time, internalising disorders, such as anxiety and depression, are thought to have increased in the last two decades, with 5.8% of CYP reporting difficulties in these areas (NHS Digital, 2018). As 50% of individuals experiencing lifetime cases of MHDs have first experienced symptoms by the age of 14, and 75% by age 18 (Kessler et al., 2005), it is clear that childhood and adolescence is a critical period for the onset of these difficulties. Thus, this creates an urgent need to better understand the processes that underpin their development.

While the exact mechanisms leading to the onset of childhood internalising disorders are not known, it is generally theorised that a complex interaction of multiple biological, social, psychological, and environmental factors contribute to their development (Bernaras et al., 2019). Specifically, in terms of CYP, it is also hypothesised that endocrine alterations, such as age-related changes and factors associated with puberty, may make them more vulnerable to MHDs (Bernaras et al., 2019). Conversely, Curley et al. (2011) argue that it is the quality of the social environment that influences the development and activity of neural systems that impact on the onset of such disorders. However, whilst the factors contributing to the development of these difficulties are disputed, previous functional magnetic resonance imaging (fMRI) studies consistently demonstrate altered neural activation in CYP experiencing anxiety and depression. It has been suggested that as adolescence is characterised by a period of rapid cortical maturation of

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neural areas involved in emotional processing, emotion regulation, and reward processing, factors that cause this development to be altered or interrupted may underpin the onset of MHDs in a way that is distinct from the mechanisms underlying adult-onset disorders (Kerestes et al., 2014).

For instance, Hulvershorn et al's. (2011) systematic review identified alterations to a corticolimbic network of key areas that mediate the emotional dysregulation associated with adolescent major depressive disorder (MDD). This includes functional abnormalities in the hippocampus, pre-frontal cortex (PFC), and amygdala. Abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) due to the overproduction of adrenocorticotropic hormone in the anterior pituitary, and increased glucocorticoid release from the adrenal glands, are thought to result in damage to hippocampal neurons (Jacobs et al., 2000; Sapolsky et al., 1990). Conversely, functional abnormalities in the anterior cingulate (ACC), dorsolateral and orbitofrontal cortex regions of the PFC are considered to have implications for self-referential processing and mood stabilising via interactions with limbic and striatal nodes (Pizzagalli, 2011). Finally, while abnormalities in amygdala activation have consistently been identified, the type of alteration has differed, and varies according to the task presented (Hulvershorn et al., 2011). However, increased amygdala activation generally appears to bias perception towards a negative emotional valence in individuals with depression (Hulvershorn et al., 2011), particularly in facial recognition tasks (Fu et al., 2004; Sheline et al., 2001; Whalen et al., 2002).

In terms of anxiety, according to Blackford and Pine's review (2012), the amygdala has consistently been shown to play an important role in CYP anxiety disorders. Specifically, the most common finding is increased activation in this region, particularly when viewing negative emotional expressions (Guyer et al., 2008; Hare et al., 2008; C. S. Monk et al., 2003). In addition, children with generalised anxiety disorder (GAD) have been found to show differences in functional connectivity between the amygdala and other brain regions, such as the insula and ventrolateral PFC (vlPFC: McClure et al., 2007; C. Monk et al., 2008). For instance, lower vlPFC activation has been found to be associated with anxiety severity, suggesting dysfunction in vlPFC regulation of the amygdala. Abnormalities in PFC activation, including the vlPFC and dmPFC, have frequently been implicated in childhood anxiety disorders, although the direction of the effect varies by the type of task presented (Blackford and Pine, 2012). Finally, similarly to research surrounding depression, a review by Iorfino et al. (2016) noted reduced ACC structure and function and HPA dysregulation in youth with anxiety disorders.

Thus, it appears that several brain regions are involved in the presentation of both depression and anxiety in CYP, which is not too surprising given that the National Comorbidity Survey (NCS) rated lifetime comorbidity as high as 58% (Melton et al., 2016). However, there is a paucity of research systematically and rigorously comparing differences in activation between the two internalising disorders in CYP (Melton et al., 2016). Furthermore, the reviews that have examined neural dysfunction in either anxiety or depression are somewhat dated (e.g., Blackford and Pine, 2012; Hulvershorn et al., 2011; Kerestes et al., 2014), which is pertinent given the recent increase in internalising disorders amongst CYP (NHS Digital, 2018). In addition, while Kerestes et al's. (2014) review systematically examined functional differences in youth with MDD, this only included participants aged 13–25, and so information regarding younger CYP was missed. Given that half of MHDs first present symptoms before the age of 14 (Kessler et al., 2005), this is an important age group to examine. Conversely, Hulvershorn et al. (2011) only reported differential activation by task type, and so over-arching areas of dysfunction were not identified. In terms of anxiety disorders, it appears that relatively less research has been conducted with CYP in this area, and while Blackford and Pine (2012) did present a literature review on this topic, it was not systematic.

Specifically, there are limited meta-analyses utilising Activation Likelihood Estimation (ALE) to examine differential neural processes associated with internalising disorders in CYP. While one ALE study (Miller et al., 2015) has been conducted with MDD in youth, finding hyperactivation in the subgenual anterior cingulate cortex and vlPFC, no comparisons were made with anxiety disorders and inclusion criteria incorporated young adults up to age 24. Therefore, the present study aims to conduct separate ALE analyses of neuroimaging studies that have examined anxiety and depression across CYP only, to enhance knowledge of the neural processes involved. In line with this, another aim is to identify areas of common activation and deactivation in MDD and anxiety due to co-morbidity. A final aim is to compare activation and deactivation in relation to the specific tasks employed in functional brain imaging studies, in order to elucidate specific processes (e.g. cognitive vs. affective tasks).

2. Methods

2.1. Literature search

A computerised search using the databases PubMED and PsycINFO was conducted, covering the periods from January 2001 to January 2020. Grey literature was also searched (e.g. government reports, policy statements and issues papers, conference proceedings). Search terms were (* = truncated): (fMRI OR MRI OR brain imaging OR magnetic resonance imaging) AND (child* or adolescen*) AND (depression OR anxi*). January 2001 was chosen as the start date for this review, as the first neuroimaging study in adolescent MDD was published in this year (see previous review by Kerestes et al., 2014). Additional filters were utilised to refine the search further; these included: age (child or adolescent), human participants, English language, and journal article only. Searches were conducted on titles and abstracts.

2.1.1. Inclusion and exclusion criteria

Studies were included if they: a) used task-based fMRI, b) were conducted with school age CYP (4–18), c) included participants with a diagnosis of MDD and/or an anxiety disorder (generalised, social, separation, or panic disorder) using recognised diagnostic criteria (in accordance with DSM-IV; APA, 2013), d) included a comparison group of healthy controls, e) reported the neural activation or deactivation co-ordinates in Montreal Neurological Institute (MNI) or Talairach space, f) assessed brain regional activation and deactivation using contrast analyses and not regression models, g) were published in English, and h) were published in a peer-reviewed journal article.

2.1.2. Selected studies

The literature searches yielded a total of 896 studies. After the application of the above criteria, and the removal of duplicates, 739 studies were excluded. Of the 157 remaining eligible studies, a further 109 studies were excluded as they failed to provide all necessary information. Thus, there were 48 eligible studies that contributed to the meta-analyses (see Table 1). Paradigms were varied (preventing separate analyses of tasks) and included: attention (e.g. sustained, facial stimuli); emotion matching; implicit fear; reward paradigms; self-perception; Go/No-Go response inhibition; Cyberball peer interaction; Iowa Gambling Task (risky decision-making); monetary decision-making and emotion regulation tasks.

2.2. fMRI methods

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive brain imaging technique that indirectly measures neuronal activation by way of Blood Oxygen Level Dependency (BOLD). fMRI studies employ either a Whole Brain (WB) or a Region of Interest (ROI) approach. In a WB approach, significant activation clusters are calculated by comparing globally across the whole brain, independently of threshold limitations. In contrast, an ROI analysis employs a masque or small volume correction, to add or remove a region of the brain during

Table 1
Included studies.

Study name	Disorder	Task type	Sample size		Age range	Mean age (SD)		Analysis	Activation	N foci
			Clinical	HC		Clinical	HC			
Halari et al. (2009)	MDD	Attention	21	21	14–17	16.2(0.83)	16.3 (1.1)	WB	Deactivation	9
Henderson et al. (2014)	MDD	Facial-emotion matching	19	18	12–20	17.3(2.4)	15(1.5)	WB	Deactivation	3
Ho et al. (2014)	MDD	Implicit fear facial affect recognition	26	37	13–17	15.8(1.4)	16.1 (1.2)	WB	Deactivation	3
Sharp et al. (2014)	MDD	Reward anticipation	14	19	10–16	13.42(1.78)	13.71 (1.85)	ROI	Deactivation	2
Blom et al. (2015)	MDD	Emotional face processing	31	36	13–18	16	16.1	WB	Activation	9
Bradley et al. (2016)	MDD	Self-perception word task	23	18	12–20	16.62(2.51)	16.12 (1.54)	WB	Activation	2
Chuang et al. (2016)	MDD	Go/no-go	82	24	12–17	15.72(1.10)	15.89 (1.42)	WB	Activation	1
Diler et al. (2013)	MDD	Emotional face processing	10	10	12–17	15.9(1.10)	15.6 (1.2)	WB	Activation	9
Diler et al. (2014)	MDD	Go/no-go	10	10	12–17	15.9(1.10)	15.6 (1.1)	WB	Activation	4
Gaffrey et al. (2013)	MDD	Emotional face processing	23	31	4–6†	5.04(0.76)	5.06 (0.89)	Both	Activation	8
Groschwitz et al. (2016)	MDD	Cyberball peer interaction	14	15		15.9(1.60)	14.5 (1.70)	ROI	Activation	1
Harms et al. (2019)	MDD	Cyberball peer interaction	87	39		14.87(1.58)	14.43 (1.51)	WB	Activation	1
Ho et al. (2015)	MDD	Facial-emotion matching	26	37	13–17	16.1(0.30)	16(0.2)	WB	Activation	7
Ho et al. (2016)	MDD	Emotional face processing	26	37	13–17	16.1(0.30)	16(0.2)	WB	Activation	6
Holt et al. (2016)	MDD	Self-referential memory	56	30	11–17	15.69(1.17)	15.76 (1.39)	WB	Activation	1
Jankowski et al. (2018)	MDD	Cyberball peer interaction	87	39	11–17	14.89(1.67)	14.43 (1.51)	WB	Activation	1
Pan et al. (2011)	MDD	Go/no-go	30	14	13–17	15.87(1.55)	15.21 (1.42)	WB	Activation	3
Pan et al. (2013a)	MDD	Emotional face processing	15	15		15.87(1.55)	15.27 (1.39)			
	WB	Activation	4							
Pan et al. (2013b)	MDD	Iowa Gambling Task	29	13	12–17	16.0(1.18)	15.15 (1.46)	WB	Activation	18
Quevedo et al. (2018)	MDD	Facial recognition	43	38		14.73(1.76)	14.46 (1.52)	WB	Activation	10
Redlich et al. (2018)	MDD	Face matching	20	21	15–18	16.0(1.03)	16.6 (1.08)	ROI	Activation	2
Roberson-Nay et al. (2006)	MDD	Facial memory encoding	10	23	8–17†	13.8(2.7)	14.8 (2.2)	WB	Activation	3
Shad et al. (2011)	MDD	Monetary decision making	22	22	12–20	15.0(2.10)	16.0 (2.10)	WB	Activation	1
Tao et al. (2012)	MDD	Emotional face processing	19	21	11–18	14.2(1.90)	14.9 (2.50)	Both	Activation	41
Chantiluke et al. (2012)	MDD	Sustained attention	20	21	13–18	16.2(0.80)	16.3 (1.10)	WB	Both	7
Forbes et al. (2009)	MDD	Reward processing	15	28	8–17†	13.5(2.10)	13.1 (2.60)	ROI	Both	7
Olino et al. (2011)	MDD	Reward anticipation	10	16	8–16†	13.31(2.49)	13.31 (2.49)	Both	Both	2
Perlman et al. (2012)	MDD	Emotion regulation	14	14	12–17	15.7(1.50)	15.1 (1.60)	Both	Both	6
Yang et al. (2009)	MDD	Stop-signal	13	13	13–17	16.0(1.50)	15.8 (1.50)	WB	Both	4
Yang et al. (2010)	MDD	Facial-emotion matching	12	12	12–17	15.9(1.40)	15.4 (1.70)	Both	Both	7
Thomas et al. (2001)	Anxiety & MDD	Emotional face processing	5 MDD; 12 anxiety	12	8–16†	12.3(2.77) MDD; 12.8(2.1) anxiety	12.1 (2.60)	ROI	Both	2
Beesdo et al. (2009)	Anxiety & MDD	Emotional face processing	26 MDD; 16 anxiety	45		14.08(2.23) MDD; 12.77(1.85) anxiety	13.93 (2.18)	ROI	Activation	5
Benson et al. (2015)	Anxiety	Monetary reward	18	20	8–18†	12.13(2.40)	13.24 (2.30)	WB	Activation	2
Carlisi et al. (2017)	Anxiety	Face attention	14	19		14.05(2.16)	14.16 (2.37)	Both	Activation	6
Galvan et al. (2014)	Anxiety	Risky decision making	17	15	8–17†	13.05(2.87)	13.69 (2.28)	WB	Activation	2
Guyer et al. (2012)	Anxiety	Monetary incentive delay	32	26		13.02(2.85)	13.99 (2.44)	ROI	Activation	1
Jarcho et al. (2015)	Anxiety	Social feedback task	15	24	8–17†	12.79(3.39)	13.68 (2.39)	WB	Activation	2

(*continued on next page*)

Table 1 (*continued*)

Study name	Disorder	Task type	Sample size		Age range	Mean age (SD)		Analysis	Activation	N foci
			Clinical	HC		Clinical	HC			
Maslowsky et al. (2010)	Anxiety	Probe detection, event-related design (facial-emotion)	14	10		13.35(2.10)	14.5 (1.40)	ROI	Activation	4
McClure et al. (2007)	Anxiety	Face-emotion rating	15	20		11.67(1.97)	12.19 (2.10)	WB	Activation	11
Monk et al. (2006)	Anxiety	Face attention	18	15	9–17†	12.28(2.05)	13.53 (2.41)	ROI	Activation	1
Smith et al. (2018)	Anxiety	Social appraisal	14	17	8–17†	13.18(3.32)	13.35 (2.94)	WB	Activation	1
Speilberg et al. (2015)	Anxiety	Cognitive peer evaluation	16	26	8–17†	12.7(3.30)	13.3 (2.80)	ROI	Activation	1
Strawn et al. (2012)	Anxiety	Continuous performance with distractors	10	10	11–17	14.3(2.0)	13.3 (3.0)	WB	Activation	2
Swartz et al. (2014a)	Anxiety	Emotional faces - shifting attention	34	35	7–19†	13.84(3.30)	15.2 (3.90)	ROI	Activation	1
Swartz et al. (2014b)	Anxiety	Facial-emotion matching	34	19	8–19†	13.94(3.20)	15.07 (4.0)	WB	Activation	20
Williams et al. (2015)	Anxiety	Anticipation	20	20	8–12†	9.8(1.20)	9.85 (1.10)	Both	Activation	9
Yin et al. (2017)	Anxiety	Emotional face processing	20	14	13–18	15.7(1.70)	15.5 (1.70)	WB	Activation	8
Guyer et al. (2008)	Anxiety	Cognitive peer evaluation	14	14		12.3(2.76)	12.58 (2.54)	Both	Both	5

MDD = major depressive disorder.
† = removed for sensitivity analyses.

statistical analysis. ROI analyses are favourable if previous studies highlight the significance of the region and tend to inflate the significance of the meta-analysis as a whole. ROI analyses were reported by some studies included in the current meta-analyses and so additional analyses were conducted to examine whether these ROI studies biased the overall findings.

2.3. Quantitative data synthesis: ALE meta-analyses

BrainMap GingerALE version 3.0.2 software (Laird et al., 2005; Turkeltaub et al., 2012) was used here. We applied the updated version of the ALE approach (Eickhoff et al., 2009) to conduct the meta-analyses using Talairach or Montreal Neurological Institute (MNI) coordinates ("foci") from neuroimaging results. Foci were extracted from publications examining children and adolescents (age range: 4 – 20 years of age), checked by two researchers (EA, SJB). Papers that reported co-ordinates in standard Talairach space were converted into MNI using the GingerALE software. Text files were then created, listing the study names, number of subjects and a list of the foci (MNI coordinates) associated with neural activation (but not deactivation) to subliminal stimuli. Specifically, we conducted five separate ALE meta-analyses: a) activation for both anxiety disorders and MDD; b) activation for anxiety disorders only; c) activation for MDD only; d) deactivation for both anxiety disorders and MDD; e) deactivation for MDD (there were not enough contributing deactivation studies to examine anxiety disorders separately). Text files of foci were cross-checked by two researchers as above. Text files for each meta-analysis are available on request.

ALE is a statistical modelling technique specifically designed to address the variance between and within fMRI studies. This technique uses the total foci coordinates reported in each study to build a 3-dimensional Gaussian kernel to provide a modelled activation (MA) map for each study. The position of foci can be a consequence of between-study variances, such as the different templates used, or the differences between participants, and as such these two main issues are considered in the parameters of the kernel. This is done by weighting the foci reported by the number of participants in each study. Finally, the MA maps for each study are combined for each separate meta-analysis, creating an experimental ALE map. This is tested against the null hypothesis that there is random variation in relation to the spatial orientation of neural activation for the specific meta-analysis (e.g. subliminal presentation of faces), but that the within-study variation is fixed. A random effect model is employed by the ALE analysis technique, which assumes a higher than chance likelihood of consensus between different experiments, but not in relation to activation variance within each study. The null distribution map is permuted by the number of studies that constitute each meta-analysis. To correct for multiple comparisons, we used a threshold of $p < 0.05$ False Discovery Rate (FDR), and chose a minimum cluster size of 100 mm3, as per most studies. We used an anatomical image overlay program called Mango (http://ric.uthscsa.edu/mango) to illustrate the results of our meta-analyses. GingerALE employs the term "contributing studies", to describe studies that are located within the boundaries of ALE cluster. However, this does not discount other studies that might be located near these boundaries but outside of the cluster, which could have also contributed to it.

2.3.1. Sensitivity analyses

Given the wide age range (4–20 years) of participants in the included studies and the neurobiological and clinical changes that occur during this period of development, sensitivity analyses were conducted to establish if any significant findings varied by age group. However, almost all studies that included children also included adolescents in one heterogeneous sample, and so no simple method of categorising studies into child and adolescent samples was available. As such, two sensitivity analyses were conducted. Sensitivity analysis 1 excluded the only study solely involving children as participants (Gaffrey et al., 2013); aged 4–6 years). Sensitivity analysis 2 excluded all studies that involved participants younger than 11 years of age, regardless of the upper age limit.

3. Results

Of the 896 fMRI studies found during searching, 739 did not meet the inclusion criteria, and 108 failed to provide all the necessary information. There was also one study that did not present co-ordinates, and these could not be obtained from the authors. Thus, there were 48 remaining studies that contributed to the five meta-analyses reported here. In the first set of meta-analyses examining activation, 45 studies were included across both types of internalising disorders; there were then 27 for the MDD analysis, and 18 for the anxiety analysis. In terms of the analyses for deactivation, 12 studies were included across both internalising disorders; there were then 11 for the MDD analysis. As

there was only one study focusing on anxiety disorders, a meta-analysis was not conducted. See Table 1 for details of included studies. The significant clusters are reported in Table 2 and sensitivity analyses in Table 3.

3.1. Meta-analysis one: significant ALE clusters for activation across internalising disorders

From 233 foci, 2169 subjects and 45 separate experiments, two clusters were found that survived the FDR correction threshold (see Fig. 1a). Cluster one was identified with two peaks in the left hemisphere and was primarily located in the amygdala (57% of studies), extending slightly into Brodmann area 34 (24.8%) and 28 (5.6%), the putamen (4.2%), the medial globus pallidus (4.2%), and the lateral globus pallidus (4.2%). Cluster two was identified with two peaks in the right hemisphere and was primarily located in the amygdala (45.6%), extending slightly into Brodmann area 34 (32.4%) and 28 (4.4%), the putamen (14.7%), and the lateral globus pallidus (2.9%). Sensitivity analysis 1 included 225 foci, 2115 subjects and 44 experiments. The coordinates of both clusters identified were identical to the main analysis. Sensitivity analysis 2 included 175 foci, 1613 subjects, and 31 experiments and identified two clusters. Cluster one was broadly similar to that in the main analysis; it consisted of two peaks in the left hemisphere and was primarily located in the amygdala (62.3%), extending into Brodmann area 34 (13.7%) and 28 (6.2%), the medial (7.5%) and lateral (4.8%) globus pallidus, and the putamen (4.8%). Cluster two was identified with four peaks in the right hemisphere and was primarily located in the putamen (52.8%), amygdala (28.3%), lateral globus pallidus (11%), and Brodmann area 34 (5.5%) and 28 (2.4%).

3.2. Meta-analysis two: significant ALE clusters for activation in anxiety disorders

From 79 foci, 719 subjects and 18 separate experiments, two clusters were found that survived the FDR correction threshold (see Fig. 1b). Cluster one was found with two peaks in the left hemisphere and was primarily located in the amygdala (55.8%), extending slightly into Brodmann area 34 (28.5%) and 28 (7.3%), and the medial globus pallidus (7.9%). Cluster two was found with two peaks in the right hemisphere and was primarily located in the amygdala (56.4%), extending slightly into Brodmann area 34 (23.8%) and 28 (7.9%), the putamen (6.9%), and the lateral globus pallidus (5%).

Sensitivity analysis 1 was not required as results of the Gaffrey et al. (2013) study pertained only to MDD. Sensitivity analysis 2 included 39 foci, 319 subjects, and 8 experiments. Two clusters were found. Both clusters were broadly similar to those identified in the main analysis. Cluster one consisted of three peaks in the left hemisphere and was primarily located in the amygdala (58.9%), medial globus pallidus (14.4%), Brodmann area 28 (13.3%) and 34 (12.2%), and the lateral globus pallidus (1.1%). Cluster two consisted of one peak in the right hemisphere and was primarily located in the amygdala (56.9%), putamen (19.6%), lateral globus pallidus (13.7%), and Brodmann area 28 (5.9%) and 34 (3.9%).

3.3. Meta-analysis three: significant ALE clusters for activation in MDD

No significant clusters were reported by the ALE analysis.

3.4. Meta-analysis four: significant ALE clusters for deactivation across internalising disorders

No significant clusters were reported by the ALE analysis.

3.5. Meta-analysis five: significant ALE clusters for deactivation in MDD

No significant clusters were reported by the ALE analysis.

4. Discussion

Findings from the present meta-analysis of 48 fMRI studies emphasise significant clusters of activation during a range of emotion-regulation and decision-making tasks in the bilateral amygdala for CYP with internalising disorders, and specifically for those with anxiety disorders. Significant activation also extended into the dorsal anterior cingulate (dACC: Brodmann area 32), entorhinal cortex (Brodmann area 28), the putamen, and the medial and lateral globus pallidus in CYP with anxiety disorders. Conversely, no significant clusters of activation were identified for the MDD group alone. Finally, no significant clusters of deactivation were found in any of the analyses.

Previous studies have shown that chronic anxiety disorders in general are associated with increased bilateral amygdala activation, according to a *neurosynth* (Yarkoni et al., 2011; http://neurosynth.org) meta-analysis of 95 studies (using the search term 'anxiety disorders'). Fig. 2 provides a comparison between our findings and the results of the neurosynth search; as can be seen, areas of activation are similar. As the neurosynth search also included studies with adult disorders, this provides some evidence that areas of neural activation in anxiety disorders are consistent across age groups. Closer inspection of seven of the neuroimaging studies that specifically examined neural activation in adolescents with anxiety disorders demonstrated that in addition to

Table 2.
Locations of MNI peak coordinates with significant ALE values.

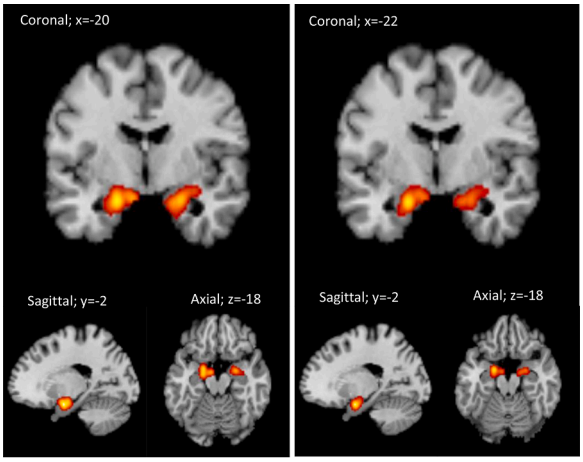
Cluster	Anatomical region	Peak	Peak voxel coordinates			Cluster size (mm^3)	ALE value ($x10^{-2}$)	Contributing experiments	
			x	y	Z			N	%
Meta-analysis 1									
1	L amygdala, parahippocampal gyrus					3904		13	29
		Peak 1	−20	−2	−18		0.034266		
		Peak 2	−10	−4	−18		0.025981		
2	R amygdala, parahippocampal gyrus, lentiform nucleus					2512		8	18
		Peak 1	22	−2	−18		0.029863		
		Peak 2	32	−6	−12		0.021728		
Meta-analysis 2									
1	L amygdala, parahippocampal gyrus, lentiform nucleus					3144		8	44
		Peak 1	−20	−2	−20		0.030207		
		Peak 2	−12	−6	−14		0.019187		
2	R amygdala, parahippocampal gyrus					1848		5	28
		Peak 1	16	−6	−20		0.019194		
		Peak 2	22	−4	−18		0.018806		

Abbreviations: ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; R, right; L, left.

Table 3
Locations of MNI peak coordinates with significant ALE values: Sensitivity analyses.

Cluster	Anatomical region	Peak	Peak voxel coordinates x	y	z	Cluster size (mm^3)	ALE value ($x10^{-2}$)	Contributing experiments N	%
Meta-analysis 1: Sensitivity analysis 1									
1	L amygdala, parahippocampal gyrus					3960		13	30
		Peak 1	−20	−2	−18		0.034266		
		Peak 2	−10	−4	−18		0.025981		
2	R amygdala, parahippocampal gyrus, lentiform nucleus					2104		7	16
		Peak 1	22	−2	−18		0.028874		
		Peak 2	32	−6	−12		0.021728		
Meta-analysis 1: Sensitivity analysis 2									
1	L amygdala, parahippocampal gyrus, lentiform nucleus					2688		8	26
		Peak 1	−20	−8	−16		0.026379		
		Peak 2	−12	−6	−14		0.018838		
2	R putamen, amygdala, lentiform nucleus, parahippocampal gryus					2112		7	23
		Peak 1	22	−2	−18		0.024095		
		Peak 2	32	−6	−12		0.021712		
		Peak 3	28	−6	4		0.01900		
		Peak 4	30	−8	−4		0.011296		
Meta-analysis 2: Sensitivity analysis 2									
1	L amygdala, parahippocampal gyrus, lentiform nucleus					2040		5	63
		Peak 1	−12	−6	−14		0.018502		
		Peak 2	−18	−8	−14		0.017712		
		Peak 3	−24	2	−26		0.0096		
2	R amygdala, parahippocampal gyrus					1048		3	38
		Peak 1	16	−6	−20		0.015996		

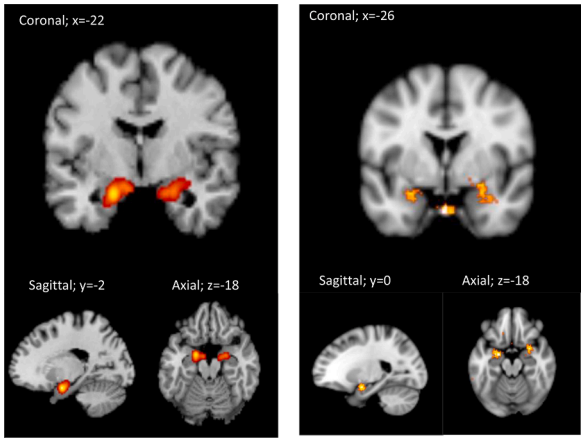
Abbreviations: ALE, activation likelihood estimation; MNI, Montreal Neurological Institute; R, right; L, left.



a. ALE results: Analysis 1 (internalising disorders)

b. ALE results: Analysis 2 (anxiety disorders)

Fig 1.. a. ALE results: Analysis 1 (internalising disorders). b. ALE results: Analysis 2 (anxiety disorders).



a. ALE results: Analysis 2 (anxiety disorders)

b. Neurosynth results (anxiety disorders)

Fig 2.. a. ALE results: Analysis 2 (anxiety disorders). 2. Neurosynth results (anxiety disorders).

amygdala activation, other brain regions during emotion-regulation and decision-making tasks were also implicated. For example, in response to uncertainty, increased anterior and posterior cingulate cortex activation was reported (Krain et al., 2008), while response to uncomfortable peer interaction increased amygdala-cingulate functional coupling, with reduced nucleus accumbens activation in anticipation of peer feedback (Spielberg et al., 2014). Moreover, amygdala and anterior hippocampus activation in response to emotional faces was associated with met versus val heterozygous BDNF polymorphism in anxious and depressed adolescents, suggesting that genetic susceptibility may underlie dysfunctional adolescent affect regulation (Lau et al., 2010). Finally, deficits in fear extinction recall are suggested to underlie anxiety disorders in adolescents; during a fear-recall fMRI task, anxiety disorders have been shown to be associated with negative functional connectivity between prefrontal cortex and limbic regions (Ganella et al., 2017).

In contrast, chronic or recurrent MDD is associated with persistent exposure to stress-induced glucocorticoids, which may have neurotoxic effects associated with amygdala shrinkage (Hamidi et al., 2004). Structural amygdala alterations may lead to reduced activation in those with MDD, given that healthy adult responses to fearful faces are probes for increased amygdala activation (Fusar-Poli et al., 2009; Hulvershorn et al., 2011). Similarly, in healthy adolescents, bilateral amygdala activation was greater when fearful faces were shown, compared to neutral expressions. Healthy *children*, on the other hand, had less amygdala activation with fearful than neutral face probes (Baird et al., 1999). These disparate findings preliminarily suggest an age-related shift toward the amygdala's sensitivity to fear in typically developing children and may provide some explanation for the lack of significant findings in the MDD group in the current meta-analysis.

Interestingly, our sensitivity analysis including studies involving only adolescents identified more frequent increased activation in the putamen than the amygdala across internalising disorders. This suggests potential differences in neural activation between younger children and

older adolescents. A possible explanation for this is the cognitive inhibition spill-over hypothesis, whereby intentional cognitive inhibition spills over to inhibit neural responses to affective stimuli (Stoycos et al., 2017). It could be that in older adolescents with a more developed (although not fully developed) prefrontal cognitive inhibition system, the cognitive inhibition spills over to inhibit amygdala responses. Indeed, previous research by Stoycos et al. (2017) into the spill-over hypothesis found that younger children had less activation in the ACC and bilateral IFG, regions that are pivotal for cognitive inhibition, suggesting this may be more likely in older adolescents. Furthermore, youths' internalising symptoms were positively associated with activation in the right pallidum and putamen, but not the amygdala. Berkman et al. (2009) earlier work supports this, finding the increased functional activity in the rIFG was linked with decreased activity in the amygdala, providing evidence for the inhibitory spill-over hypothesis. However, as only one of the sensitivity analyses in our study revealed this finding, and a smaller sample of studies was utilised, caution should be taken when interpreting our results. Further research is needed in this area.

4.1. Limitations

There are a few limitations that should be considered before identifying potential implications of this meta-analysis. First, fMRI data cannot ascertain cause or consequence, and specifically in this case, whether increased bilateral amygdala, limbic and ACC activation is a cause or a consequence of anxiety disorders in CYP. Second, the number of studies with heterogeneous samples (e.g., age, duration of illness, anxiety disorder versus MDD, type of treatment) prevent definitive conclusions, although the findings of this study correspond to current findings in the literature. More nuanced analyses were not possible due to the broad age range of participants in the studies included in our meta-analyses. Thus, future research should seek to investigate neural activation of internalising disorders in discrete age groups of CYP, so that more accurate comparisons can then be drawn between children and adolescents. Third, ALE is a 'vote-counting' meta-analytic method that determines the number of common foci across fMRI studies, corresponding to the likelihood of a specific cluster, which may introduce a higher level of false positives. That said, ALE is a robust measure that reflects and confirms the majority of the findings in the literature and helps to clarify the most significant regions of interest for further study. Finally, there were not enough studies within the different types of fMRI task or diagnostic group to run separate sub-analyses. Thus, although no significant clusters of activation were identified for the MDD group alone, this may be due to a lack of MDD foci to evidence significant findings, as opposed to a true lack of activation in these areas. Indeed, some of the foci contributing to the clusters in the internalising disorders analysis were from studies investigating MDD, suggesting some activation in these areas. This highlights the need for further studies examining the neural correlates of anxiety disorders and MDDs in CYP.

4.2. Implications and future directions

Significantly increased activation in ACC and limbic regions (particularly bilateral amygdala) to fearful and emotional fMRI tasks were observed in CYP with anxiety disorders. This is consistent with emerging evidence that indicates that greater illness severity is associated with greater grey matter reductions in the ACC in individuals with anxiety disorders (Iorfino et al., 2016). The ACC is an integrative hub for executive functions and socially driven interactions of the type associated with conflict monitoring and impulse control (Lavin et al., 2013). In adolescents with anxiety disorders, the connectivity between the ACC and amygdala alters according to age and is associated with a failure to establish effective limbic connectivity in childhood, or effective top-down affect regulation during adolescence and adulthood (Kujawa et al., 2016). As such, amygdala hypersensitivity and heightened top-down activation of the ACC may reflect hyper-regulation of limbic responses in CYP with anxiety disorders. Thus, findings from the present study help to detail the nature of anxiety as amygdala hyperactivity disorder, whilst also helping to define the distinction between the activation patterns during anxiety and depression.

The long-term negative impact of internalising disorders, such as anxiety and depression, is well established, with evidence suggesting poorer wellbeing, reduced economic and social productivity, and increased morbidity and mortality (McLaughlin, 2011). Thus, effective strategies for early identification, intervention and treatment are urgently needed, in order to reduce the likelihood of negative outcomes. Based on the findings in the present study regarding the role of the ACC, future research may want to consider studies that link common cognitive-affective responses to these neural patterns in CYP with anxiety disorders; this in turn may help to identify biomarkers for early prevention. This could be particularly useful in the field of 'personalised psychiatry', whereby neurobiological markers indicating prognosis or potential treatment targets could be used to guide treatment and help provide person-centred care (Iorfino et al., 2016). However, in order to achieve this, further research is first needed to establish the biomarkers that predict the onset of internalising disorders, the clinical utility of specific neurobiological markers, and the ability of these biomarkers to predict clinical response to pharmacotherapy.

Furthermore, results regarding increased amygdala activation in the present study may also have broader utility for practitioners in the field of CYP mental health. For example, findings can be used to inform other types of treatment, such as psychological therapies (e.g., cognitive behavioural therapy [CBT]). There is already some evidence to suggest that effective CBT treatment for anxiety disorders is associated with a reduction in anxiety symptoms and the startle response (a measure of amygdala reactivity), as well as reduced amygdala activation to negative emotional stimuli (Bakker et al., 2011). Additional research suggests that CBT may work by strengthening connections between the amygdala and prefrontal cortex regions involved in cognitive control, potentially enhancing top-down control of affective processes that are dysregulated in internalising disorders (Shou et al., 2017). Therefore, further research is needed into the types of therapy most effective at reducing amygdala activation, and the specific components of different therapies most likely to achieve this.

Finally, future research should also seek to identify areas of significant activation in other types of internalising disorders, in order to establish if similar implications could be applied. For instance, while the present study focused on MDD and anxiety disorders, other research appears to suggest similar neural activation in disorders such as post-traumatic stress disorder and bipolar disorder (Iorfino et al., 2016; Shou et al., 2017), although syntheses of these studies are lacking.

4.3. Conclusions

The present study was the first of its kind to conduct a meta-analyses utilising ALE to examine differential neural processes associated with depression and anxiety disorders in CYP. Findings revealed significant clusters of activation during a range of emotion-regulation and decision-making tasks in the bilateral amygdala for CYP with internalising disorders, and specifically for those with anxiety disorders. Significant activation also extended into the dACC (Brodmann area 32), entorhinal cortex (Brodmann area 28), the putamen, and the medial and lateral globus pallidus in CYP with anxiety disorders. This supports previous research in the field, and findings can be used to inform future research in terms of early identification of CYP with internalising disorders, as well as the development of effective pharmacological and psychological treatments.

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Declaration of Competing Interest

None.

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