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REVIEW ARTICLE

Neural effects of social environmental stress – an activation likelihood estimation meta-analysis

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Background. Social environmental stress, including childhood abuse and deprivation, is associated with increased rates of psychiatric disorders such as schizophrenia and depression. However, the neural mechanisms mediating risk are not completely understood. Functional magnetic resonance imaging (MRI) studies have reported effects of social environmental stress on a variety of brain regions, but interpretation of results is complicated by the variety of environmental risk factors examined and different methods employed.

Method. We examined brain regions consistently showing differences in blood oxygen level-dependent (BOLD) response in individuals exposed to higher levels of environmental stress by performing a coordinate-based meta-analysis on 54 functional MRI studies using activation likelihood estimation (ALE), including an overall sample of 3044 participants. We performed separate ALE analyses on studies examining adults (mean age $\geqslant$18 years) and children/adolescents (mean age <18 years) and a contrast analysis comparing the two types of study.

Results. Across both adult and children/adolescent studies, ALE meta-analysis revealed several clusters in which differences in BOLD response were associated with social environmental stress across multiple studies. These clusters incorporated several brain regions, among which the right amygdala was most frequently implicated.

Conclusions. These findings suggest that a variety of social environmental stressors is associated with differences in the BOLD response of specific brain regions such as the right amygdala in both children/adolescents and adults. What remains unknown is whether these environmental stressors have differential effects on treatment response in these brain regions.

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Introduction

A strong relationship exists between a person's social environment and their mental health (Meyer-Lindenberg & Tost, 2012). Increased rates of psychiatric disorders are consistently observed in people who have suffered abuse, deprivation, ostracism and isolation (Van Os *et al.* 2008). For example, childhood abuse and neglect have each been associated with, and are predictive of, increased risk for major depressive disorder (MDD), post-traumatic stress disorder and substance abuse later in life (Widom *et al.* 2007; Gilbert *et al.* 2009). Similarly, risk for schizophrenia has been repeatedly associated with living in larger urban areas and with migrant status, possibly due to higher levels of social competition (the 'social defeat' hypothesis; Selten & Cantor-Graae, 2005).

Functional magnetic resonance imaging (fMRI) is increasingly being used to characterize how brain responses to social and emotional stimuli may be different in high-risk individuals (Harmon-Jones & Beer, 2012). Recent fMRI studies comparing individuals who have experienced higher *versus* lower levels of stress have identified significant differences in blood oxygen level-dependent (BOLD) response in brain regions involved in social and emotional processing. One difficulty for interpreting these results, however, is the range of social stressors considered (e.g. urban upbringing, childhood trauma) and cognitive tasks (e.g. social stress, emotion recognition) that have been used. As such, it remains unclear whether different social environmental stressors increase risk for mental illness through common neural mechanisms.

To address this issue, we performed a coordinate-based meta-analysis to examine whether any brain

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regions were consistently different in high-risk individuals. This type of meta-analysis examines shared BOLD response across independent studies by quantitatively identifying brain regions consistently associated with effects of interest (Turkeltaub *et al.* 2002; Laird *et al.* 2005; Eickhoff *et al.* 2009; Wagner *et al.* 2014). We hypothesized that differences would be observed in brain regions associated with threat and negative affect in high-risk individuals compared with low-risk individuals.

Method

Using PubMed, we searched for fMRI studies reporting differences in BOLD response associated with exposure (in adulthood or childhood) to social environmental stress. Studies published until June 2015 were searched for with the following search term: ('functional magnetic resonance imaging' OR 'functional MRI' OR 'fMRI') AND ('social stress' OR 'early life stress' OR 'developmental trauma' OR 'childhood trauma' OR 'childhood maltreatment' OR 'urban upbringing' OR 'urbanicity' OR 'social status' OR 'socioeconomic status' OR 'ethnic minority' OR 'ostracism' OR 'rejection' OR 'exclusion') NOT Review. This resulted in 307 studies being identified in total, of which 42 were original studies that matched study criteria (a human fMRI study examining main effects on BOLD response of one or more of the social environmental stressors listed in the search term). An additional six studies were recommended by reviewers. Next, we reviewed the references from each of the papers identified. This additional search retrieved a further six studies matching criteria and with available information. In total, 54 studies meeting search criteria were retrieved. Fig. 1 lists the number of studies included and excluded in this meta-analysis, and the reasons for inclusion or exclusion.

Next, we used the activation likelihood estimation (ALE) method in GingerALE 2.3 (Laird *et al.* 2005; Eickhoff *et al.* 2009; Eickhoff *et al.* 2012; Turkeltaub *et al.* 2012) to perform a meta-analysis to determine whether any specific brain regions were consistently associated with exposure to social environmental stress. Where cluster coordinates were presented in Talairach space, these were converted to Montreal Neurological Institute (MNI) space using GingerALE ['Talairach to MNI (SPM)' transform] to input into the meta-analysis.

Maps of altered BOLD response were created for each study by modelling individual coordinates as Gaussian functions. The width of each of these functions is calculated by GingerALE software based on each study's sample size, i.e. GingerALE will model coordinates as wider Gaussian functions for loci from larger studies. Next, the overlap between these maps was used to calculate an ALE map. The probability of finding a particular value within an ALE map across studies was used to create a *p*-value image, which was thresholded using a false discovery rate of $p < 0.05$ and cluster-thresholded using 1000 threshold permutations and a cluster-level threshold of $p < 0.05$. We performed an ALE analysis of studies examining adults (mean age $\geqslant$18 years) and children and/or adolescents (mean age <18 years) separately, to examine effects of social environmental stress at different developmental stages. We also performed a contrast analysis to examine differences between environmental effects on children/adolescents *versus* adults. For this contrast analysis, we also used a false discovery rate of $p < 0.05$ and cluster-thresholded using 1000 threshold permutations.

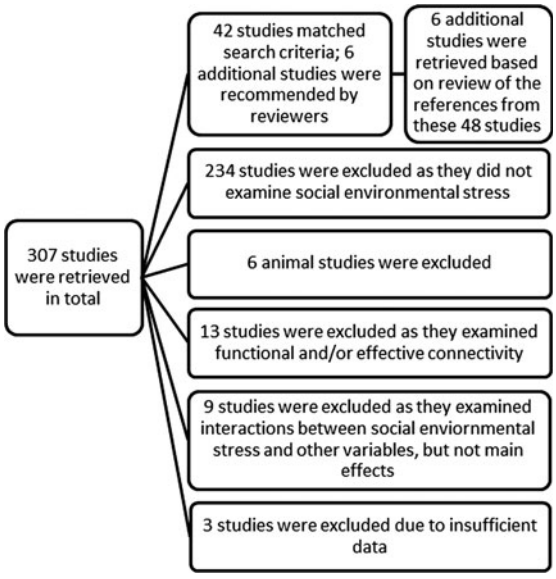

Fig. 1. Studies included and excluded from activation likelihood estimation meta-analysis.

Results

In total, 54 studies meeting search criteria were retrieved, including a total sample of 3044 participants (see Fig. 1 and online Supplementary Tables S1 and S2). Where studies or analyses used overlapping samples, we used the smaller sample to calculate the Gaussian functions, as this is a more conservative approach (S. Eickhoff, personal correspondence).

Studies varied in terms of social environmental stressors investigated and tasks used, though some studies reported similar stressors and tasks. For example, the most frequently examined stressor was 'childhood trauma' or 'childhood maltreatment' (12 studies), followed by 'early life stress' (five studies) and 'socio-economic status' (five studies). The most

frequently used task was facial emotion recognition (22 studies).

Across all studies, 55.49% of participants were adults (mean age ⩾18 years) and 44.51% of participants were children and/or adolescents; 51.97% of participants across 52 of the studies were listed as male, and 48.03% of participants were listed as female (however, gender information for the final sample included in the analysis after quality control was not provided for two studies (Dannlowski *et al.* 2012, 2013; Hsu *et al.* 2010). A total of 27 studies used negative emotional stimuli, seven used positive emotional stimuli, 12 used a mix of negative, positive and/or neutral emotional stimuli, seven used cognitive tasks, and one used a task containing both emotional and cognitive conditions of interest (see online Supplementary Tables S1 and S2).

ALE meta-analysis results – adult studies

We first performed an ALE meta-analysis that included all 34 identified adult studies (1703 participants), irrespective of participant status as a patient, healthy volunteer or combat veteran, and in the case of patients, irrespective of diagnosis. Of the participants included in this analysis, 27.95% were patients, 1.64% were combat veterans and 70.40% were healthy volunteers. This analysis identified eight separate clusters in which BOLD response differed in groups exposed to greater social environmental stress (see Table 1 and Fig. 2). Clusters incorporated the bilateral amygdala, left superior frontal gyrus, left precuneus, left putamen, left thalamus, left insula and left inferior frontal gyrus. The cluster showing differences in BOLD response across the largest number of separate empirical studies was located at the right amygdala (nine studies). In the right amygdala cluster, increased BOLD response in the risk group compared with the non-risk group was reported across all studies except one. The single study, by Boecker *et al.* (2014), which showed decreased BOLD response may have differed from the other six studies by reporting decreased BOLD response in this region during reward anticipation (a happy face symbol indicating a reward), rather than presentation of overt emotional stimuli (emotional faces, social stress, pleasant music).

Given that 13 of the 34 studies reviewed included patient participants, and in one case, combat veterans, we re-ran the ALE meta-analysis on the 21 studies that only included healthy civilian participants (1099 participants). Clusters incorporating the amygdala, thalamus and insula, identified in the first part of our analysis, again showed significant differences in BOLD response (and in the same direction) based on a comparison of participants with a history of high *versus* low environmental stress (see Table 2 and Fig. 3). The most consistent differences in BOLD response were again observed for the right amygdala (seven studies).

ALE meta-analysis results – children/adolescent studies

Analysis of 21 studies examining children/adolescents (mean age <18 years; 1341 participants) revealed six clusters showing significant overlap between studies, incorporating the bilateral amygdala, left superior temporal gyrus, right middle temporal gyrus, right cerebellum and right thalamus (see Table 3 and Fig. 4). The cluster showing differences in BOLD response across the largest number of separate empirical studies was located at the right amygdala (eight studies). Across all eight studies, the high-risk group showed increased amygdala BOLD response compared with the low-risk group.

ALE meta-analysis results – contrast between adult studies and children/adolescent studies

Contrast analysis comparing sets of foci for the adult studies and children/adolescent studies revealed no statistically significant differences.

Discussion

This study used ALE meta-analysis to investigate whether the neural effects of social environmental stress were consistent and reproducible based on fMRI studies to date. Based on this analysis, brain regions including the right amygdala showed a consistent pattern of increased BOLD response to emotional stimuli in groups with a history of social environmental stress across multiple studies and at multiple developmental stages.

Findings of increased BOLD response in the amygdala are consistent with fMRI studies reporting increased neural response of this region during negative affective states and in psychiatric illness compared with controls. For example, amygdala hyperactivity has previously been associated with trait anxiety (Etkin *et al.* 2004; Sehlmeyer *et al.* 2011), faster processing of negative stimuli and decreased levels of psychological well-being (Van Reekum *et al.* 2007), depressive symptom severity (Gaffrey *et al.* 2011) and cognitive biases towards negative stimuli (Dannlowski *et al.* 2007*a*, *b*). Increased amygdala BOLD response has also been reported in response to emotional stimuli in patients diagnosed with bipolar disorder, MDD, social anxiety disorder and borderline personality disorder when compared with healthy controls (Yurgelun-Todd *et al.* 2000; Surguladze *et al.* 2005; Minzenberg *et al.* 2007; Evans *et al.* 2008).

Table 1. *Brain regions showing differences in blood oxygen level-dependent response associated with social environmental stress – adult studies (ALE meta-analysis includes all studies irrespective of whether patient groups were included)*

Cluster	Brain region	Volume, mm^3	ALE value	MNI coordinates: x, y, z			No. of studies (foci)
1	Amygdala	2408	0.036423076	20	−4	−14	9 (11)
2	Superior frontal gyrus/Brodmann area 8	800	0.019910347	−8	52	38	2 (6)
3	Precuneus/Brodmann area 7	776	0.026976801	−22	−48	50	3 (5)
4	Putamen	472	0.017731423	−14	12	−10	3 (4)
	Subgenual anterior cingulate/Brodmann area 25		0.015727751	−2	14	−12	
5	Parahippocampal gyrus/Brodmann area 28	360	0.023307921	−18	−4	−16	3 (3)
6	Thalamus	360	0.022023844	−10	2	4	1 (3)
7	Insula/Brodmann area 13	328	0.023216197	−46	4	−4	1 (2)
8	Inferior frontal gyrus/Brodmann area 9	312	0.017854419	−44	14	22	2 (2)

ALE, Activation likelihood estimation; MNI, Montreal Neurological Institute.

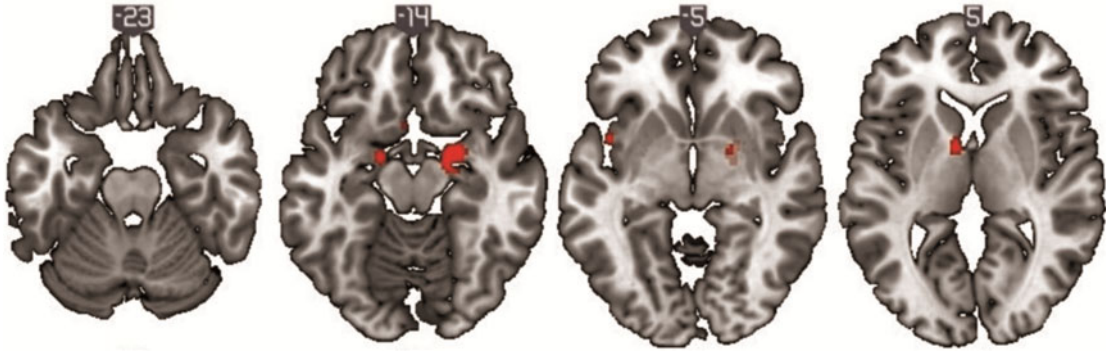

Fig. 2. Brain regions showing differences in blood oxygen level-dependent response in groups exposed to social environmental stress – all adults. Activation likelihood estimation meta-analysis includes all adult studies irrespective of whether patient groups were included. Each two-dimensional axial slice is labelled with a Montreal Neurological Institute coordinate. Clusters are rendered on the 'ch256' brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of the figure (e.g. changing the size/resolution) was performed using MS Paint and Paint.NET v3.5.10.

Table 2. *Brain regions showing differences in blood oxygen level-dependent response associated with social environmental stress – adults (ALE meta-analysis includes only studies that examined healthy volunteers)*

Cluster	Brain region	Volume, mm^3	ALE value	MNI coordinates: x, y, z			No. of studies (foci)
1	Globus pallidus	2336	0.031469878	22	−2	−14	7 (11)
2	Thalamus	472	0.022004513	−10	2	4	1 (3)
3	Insula/Brodmann area 13	400	0.022827262	−46	4	−4	2 (3)

ALE, Activation likelihood estimation; MNI, Montreal Neurological Institute.

Another cluster showing increased BOLD response across multiple adult studies with increasing stress incorporated the superior frontal gyrus/Brodmann area 8 (see Table 1). BOLD response in this region increases with increasing decision uncertainty, which may be higher in high-risk individuals during tasks involving social stimuli (Volz *et al.* 2005). Other brain regions highlighted by our analysis play an important role in processing social stimuli themselves, which might also be associated with chronic social stress.

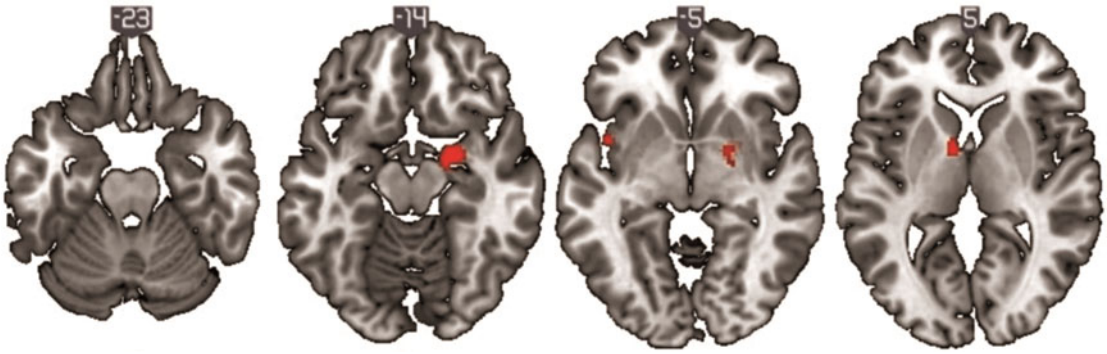

Fig. 3. Brain regions showing differences in blood oxygen level-dependent response in groups exposed to social environmental stress (healthy adults only). Activation likelihood estimation meta-analysis includes only studies that examined healthy volunteers. Each two-dimensional axial slice is labelled with a Montreal Neurological Institute coordinate. Clusters are rendered on the 'ch256' brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of the figure (e.g. changing the size/resolution) was performed using MS Paint and Paint.NET v3.5.10.

Table 3. *Brain regions showing differences in blood oxygen level-dependent response associated with social environmental stress – children/adolescents*

Cluster	Brain region	Volume, mm^3	ALE value	MNI coordinates: x, y, z			No. of studies (foci)
1	Amygdala	2456	0.05817374	20	−6	−18	8 (15)
2	Globus pallidus	1880	0.04618657	−18	−14	−12	4 (11)
	Parahippocampal gyrus/Brodmann area 28		0.027668297	−18	−4	−20	
3	Superior temporal gyrus/Brodmann area 38	832	0.038757984	−38	14	−36	1 (6)
4	Middle temporal gyrus/Brodmann area 22	456	0.026722496	62	−32	4	2 (5)
5	Cerebellum	416	0.033058073	48	−62	−50	1 (4)
6	Thalamus	328	0.029014302	18	−6	2	1 (3)

ALE, Activation likelihood estimation; MNI, Montreal Neurological Institute.

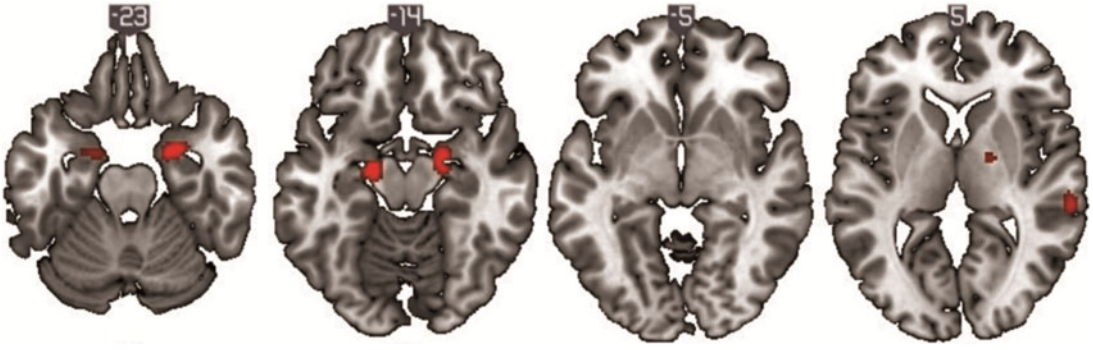

Fig. 4. Brain regions showing differences in blood oxygen level-dependent response in groups exposed to social environmental stress (children/adolescents). Activation likelihood estimation meta-analysis includes only studies that examined children/adolescents. Each two-dimensional axial slice is labelled with a Montreal Neurological Institute coordinate. Clusters are rendered on the 'ch256' brain template using MRIcroGL (http://www.mccauslandcenter.sc.edu/mricrogl/). Additional editing of the figure (e.g. changing the size/resolution) was performed using MS Paint and Paint.NET v3.5.10.

These include the precuneus, inferior frontal gyrus, superior temporal gyrus and middle temporal gyrus (see Tables 1–3) (Adolphs, 2001; Spreng *et al.* 2009; Van Overwalle, 2009). Differences in BOLD response of striatal regions were also observed in high-risk individuals across studies (see Tables 1–3). These regions,

including the putamen and globus pallidus, are heavily influenced by dopamine, which is known to increase in response to psychological stress, and may account for some of these effects (Pruessner *et al.* 2004; Selten *et al.* 2013).

The therapeutic effects of psychological and pharmacological interventions are hypothesized to be partially mediated via a normalization of brain response to emotional stimuli (e.g. of the amygdala; Fu *et al.* 2004; DeRubeis *et al.* 2008; Norbury *et al.* 2009; Rawlings *et al.* 2010; Windischberger *et al.* 2010). Our study suggests that having a history of prolonged exposure to a stressful social environment may have important neural effects on regions associated with responding to stressful stimuli and illness risk and may therefore potentially mediate these therapeutic effects. Consistent with this view, some studies have already suggested that antidepressant response in MDD patients may be mediated by a history of childhood trauma (e.g. Nemeroff *et al.* 2003). Confirming whether categorizing patients according to early adversity can help predict response to treatment type or even modality (pharmacological *versus* psychological *versus* both) will be an important avenue for further study.

Although neurobiological effects of social stress were not the focus of this meta-analysis, it is interesting to speculate about the relationship between differences in neurochemical response, given the wealth of evidence that (social) threat-related processing in the brain results in increased downstream levels of glucocorticoids in the blood (Belmaker & Agam, 2008). The amygdala, cingulate and hippocampus are particularly high in glucocorticoid receptors and are also associated with chronic cortisol secretion (Gold *et al.* 2002). Since social environmental stress causes lasting changes in hypothalamic–pituitary–adrenal (HPA) axis responsiveness to stress, including increased levels of cortisol, this could be one mechanism by which it affects BOLD response in these brain regions (Heim *et al.* 2000; Lee *et al.* 2005; Belmaker & Agam, 2008; Heim *et al.* 2008; Heim & Binder, 2012).

Another complimentary mechanism by which social stress may affect BOLD response in these brain regions is through differences in immune function. Hormones increased by psychological stress (cortisol, adrenaline) have significant effects on the immune system, enhancing pro-inflammatory cytokine responses and pro-inflammatory gene expression (Eisenberger & Cole, 2012). Inflammation, in turn, is associated with hyperactivity of both the amygdala and anterior cingulate in response to emotional stimuli, neural responses that have been correlated in the same studies with social disconnection and mood deterioration, respectively (Harrison *et al.* 2009; Inagaki *et al.* 2012).

With regard to possible gender effects, DeSantis *et al.* (2011) report differing effects of early-life trauma on HPA axis functioning in males and females, and brain regions reported in this meta-analysis, such as the amygdala, are known to function differently in males and females in response to threatening social stimuli (Schneider *et al.* 2011), suggesting that results may differ between males and females. This meta-analysis included studies that examined both males and females (44 studies), males exclusively (five studies) and females exclusively (three studies). However, only two of these studies reported different effects of social environmental stress between males and females (Felmingham *et al.* 2010, in which trauma-exposed women showed increased brainstem BOLD response compared with trauma-exposed men and Spielberg *et al.* 2015, in which effects of socioeconomic status on cingulate BOLD response were only observed in females). This research could therefore be extended by further studies comparing effects of social environmental stress between males and females, and more studies examining one gender specifically (to contrast in future meta-analyses).

A majority of the studies included investigated the effects of social stressors occurring in childhood (only 10 studies included social stressors experienced in adulthood). While this follows the widely held expectation that childhood adversity will have neurodevelopmental consequences, whether and how the duration and staging of these stressors mediated the effects observed was therefore not possible to evaluate in this meta-analysis. Answering this question will be an important priority for future meta-analyses as more studies examining effects of social stressors experienced in adulthood become available.

It is important to note that social environmental effects on BOLD response may be influenced by the types of tasks used (e.g. emotional *versus* cognitive tasks, positive emotion *versus* negative emotion). For example, Dannlowski *et al.* (2013) report effects of childhood trauma on increased limbic BOLD response during sad face processing compared with happy face processing. Similarly, limbic hyper-responsiveness has consistently been observed in psychiatric disorders in response to negative stimuli, while responses to positive stimuli are not as well characterized (Rauch *et al.* 2000; Siegle *et al.* 2007; Mothersill *et al.* 2014). Given that a minimum of 15 studies should be included in each group in an ALE contrast analysis for valid results, we could not in this study compare different types of task (Wagner *et al.* 2014).

Our meta-analysis excluded studies where the neural effects of social stress were not presented as main effects, but only reported in interaction with other variables (e.g. genetic risk, oxytocin administration).

Examining gene × environment interactions is clearly a priority for the field to determine the degree to which established environmental and genetic risk factors converge on the same neural circuits in psychiatric illness (Meyer-Lindenberg & Tost, 2012). For example, Streit *et al.* (2014) report that individuals who were both raised in an urban environment and who carried two copies of the neuropeptide S receptor 1 gene showed increased right amygdala BOLD response during stress processing, relative to individuals who grew up in highly urbanized environments with one or no copies of this variant. As further studies of the neural effects of gene by (social) environmental risk emerge, it will be interesting to determine how genetic background increases liability to, or resilience against, the neural effects of the early social environment.

Finally, although the focus of this meta-analysis was of BOLD response data during cognitive–emotional tasks, it is important to note that chronic environmental stress may also be associated with structural differences in the brain regions identified. For example, Dannlowski *et al.* (2012) showed that childhood trauma was associated with decreased hippocampal and prefrontal grey matter volumes, while Tottenham *et al.* (2010) have shown that children adopted out of orphanages at older ages had larger amygdala volumes compared with early-adopted children and controls.

In conclusion, this meta-analysis examined fMRI studies of social environmental stress exposure in both adults and children/adolescents. Social environmental stress was found to be associated with altered BOLD response across a range of brain regions, and, of these, increased BOLD response of the right amygdala was a robust finding across a range of populations and based on response to a variety of stimuli. What remains unknown is whether social environmental stress has differing effects on treatment response in these brain regions.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291716000477

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Declaration of Interest

None.

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