Review article

The brain under stress—A systematic review and activation likelihood estimation meta-analysis of changes in BOLD signal associated with acute stress exposure

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ABSTRACT

Psychosocial stress is an omnipresent phenomenon whose neural correlates in humans are still poorly understood. Several paradigms have been developed to induce acute stress in fMRI settings, but it is unclear whether there is a global brain activation pattern related to psychosocial stress. To integrate the different neuronal activation patterns, we conducted an activation likelihood estimation analysis on 31 studies totaling 1279 participants. Studies used the ScanSTRESS, Montreal Imaging Stress Test, aversive viewing paradigm (AVP), Social-Evaluative Threat or Cyberball. The analysis revealed bilateral activation clusters comprising the claustrum, insula and inferior frontal gyrus. This indicates that exposure to psychosocial stress leads to activations in brain areas involved in affective processing and the endocrine stress response. Furthermore, in a systematic review, Cyberball and AVP presented themselves as outliers due to increased activation in motor areas and lack of induction of stress related activity changes, respectively. As different paradigms emphasize different dimensions of psychosocial stress such as social evaluation or performance pressure, future research is needed to identify differences between the paradigms.

1. Introduction

Stress is experienced by everyone in their life. Giving a presentation, meeting a deadline or applying for a job all induce a stress response. Stress exerts its influence on the information processing stream at all levels from perception (e.g. Ileri-Gurel et al., 2013), over attention (e.g. Hoskin et al., 2014) and working memory functions (e.g. Diamond, 2013) to long-term memory processes (e.g. Wolf, 2017). It is however still debated how situations with different perceptual aspects and demands can elicit the same feeling of stress and how brain activation patterns are influenced by acute stress.

Stress processing starts in the brain, where the stressor and the available resources of coping with the stressor are evaluated (Lazarus, 1993). If this so-called appraisal leads the organism to conclude that the stressor poses a threat, the body reacts with two different physiological stress responses. The first response is organized by the sympathetic branch of the autonomic nervous system. The lateral hypothalamus and brainstem activate sympathetic preganglionic neurons in the spinal cord

that innervate chromaffin cells in the adrenal medulla which release epinephrine and norepinephrine into the blood stream (Joëls and Baram, 2009). As these catecholamines cannot pass the blood-brain barrier, their actions are paralleled in the brain through the release of norepinephrine by the locus coeruleus (Morilak et al., 2005). The activation of the sympathetic adrenomedullary system typically leads to an increase in heart rate, breathing frequency and sweating as well as feeling of being stressed (Mason, 1968).

The second stress response consists of the activation of the hypothalamus-pituitary-adrenal cortex (HPA) axis. Corticotrophin-releasing hormone and arginine vasopressin from the hypothalamus trigger the release of adrenocorticotropin hormone (ACTH) from the pituitary (de Kloet et al., 2005). ACTH in turn causes the adrenal cortex to release glucocorticoids, mainly cortisol in humans, into general circulation, which interacts with all body cells (Joëls et al., 2008).

What we know about brain mechanisms involved in the stress response mainly comes from animal studies, which show an involvement of limbic structures in the regulation of the stress response

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(Herman et al., 2016). With the emergence of fMRI imaging techniques, it has become possible to also study stress processing in the human brain. Several paradigms have been devised in recent years for acute stress induction in the MRI environment, and most of these lead to an activation of the HPA axis. As different stress induction paradigms set out to do the same thing – namely induce stress – one would expect these paradigms to show similar activation patterns in the brain. However, it is unclear how brain activity patterns associated with these paradigms resemble or differ from each other.

A recent meta-analysis by Kogler et al. (2015b) compared activation patterns in the brain in response to psychological and physiological stress. Although both types of stressors elicit similar hormonal and subjective responses, only activation in the inferior frontal gyrus and the anterior insula showed overlapping activation. Physiological stress additionally led to activation in the insula, striatum and middle cingulate cortex, while psychological stress was accompanied by activation of the right superior temporal gyrus and deactivation of the striatum. In their analysis, Kogler et al. (2015b) focused on pain as a physical stress stimulus as it is a reliable stressor and well established in the MRI environment. However, as psychological stressor, the authors included different stress induction paradigms in their study without differentiating between them. Studying similarities and differences in brain activation between paradigms inducing psychosocial stress is however crucial to achieve an advanced understanding of the underlying neural correlates of the acute stress response. The most common psychosocial stress induction paradigms in the scanner are inspired by the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), which is a widely used paradigm to induce stress in the laboratory. The TSST consists of a speech and a mental arithmetic task in front of a socially unresponsive committee. This paradigm is especially appropriate to elicit a stress response as it combines the most successful features that induce stress: in a landmark meta-analysis, Dickerson and Kemeny (2004) concluded that tasks containing uncontrollability and social-evaluative threat as well as a performance component lead to the largest increase in HPA axis activity as well as the longest recovery period. This suggests that MRI suitable paradigms that include these elements as well have a strong probability of eliciting a stress response similar in strength. A recent study that gave an overview of the aptitude of these stress induction methods concluded that the Montreal Imaging Stress Test (MIST) and the Aversive Viewing Paradigm (AVP) reliably elicit a stress response while the ScanSTRESS paradigm poses a promising new approach to the study of stress (Noack et al., 2019). On the other hand, the authors concluded that the Social Evaluative Threat (SET) needs more research to prove its effectiveness and validity.

The diversity of neuroimaging stress induction paradigms yields two important questions that have not been answered yet: (1) whether there is a generalized brain response to psychosocial stress regardless of stress induction paradigm and (2) it is unclear to what extent the brain activation elicited by different paradigms overlap. Regarding these aims, it is important to point out that earlier work by Kogler et al. (2015b) focused mainly on the differences between psychological and physiological stress. However, possible commonalities and differences between methods of psychosocial stress have not been addressed. Answering these questions is crucial for understanding the neurobiological foundation of the psychosocial stress response. For this purpose, we performed (1) a systematic review on the available literature and (2) an activation likelihood estimation (ALE) analysis (Eickhoff et al., 2012). While the ALE meta-analysis can provide insights into global brain activation patterns across stress induction paradigms in the scanner, it is not possible to elucidate specific patterns associated with each individual paradigm separately between the different paradigms due to the low number of studies. To illuminate on this matter, we conducted a systematic review in which we focus on the individual paradigms and their differences, namely the ScanSTRESS, MIST, SET, AVP and Cyberball.

2. Methods

2.1. fMRI stress paradigms

Several different stress induction paradigms are used in the scanner environment.

In the aversive viewing paradigm (AVP), participants are shown movie clips while in the scanner (e.g. Henckens et al., 2009). The aversive video material shows disturbing violent content from a distressing movie, while the control video material stems from a neutral movie scene. Participants are asked to watch the movies attentively and imagine themselves in the scene from an eyewitness perspective. This leads participants to perceive the movie clips as unpredictable and uncontrollable leading to a stress response.

In the social-evaluative threat (SET) paradigm, participants are asked to prepare a speech that will be audiotaped and judged by peers on how persuasive, organized and intellectual the participant is. After a 2-minute baseline period in the scanner, participants are prompted with the topic of the speech and are given 2 min preparation time before they are informed that that they will not have to give the speech (e.g. Eisenbarth et al., 2016). Thus, this paradigm is based on the anticipation of social judgement and the resulting stress response.

The Montreal Imaging Stress Test (MIST) consists of a mental arithmetic task, a control and a rest condition in the scanner (Dedovic et al., 2005). Participants have to solve math problems of varying difficulty under time constraints, while performance indicators on screen imply that participant's performance is below average. Difficulty and time limit are adapted so that a range of 20 %–45 % correct answers is enforced. During the control condition, no time constraints and performance indicators are shown.

The ScanSTRESS paradigm is a more recent tool for stress induction in the MRI environment (Lederbogen et al., 2011; Streit et al., 2014). Participants perform challenging serial subtraction and mental rotation tasks under time pressure while a window on screen shows a live feed of a jury panel providing negative feedback on the participants' performance. The life feedback mimics the negative social feedback presented in other stress induction paradigms like the Trier Social Stress Test and distinguishes this paradigm from the others listed here. The stress and control condition are presented alternately in a block design. During the control condition, participants perform simple number and figure matching tasks without any feedback from the jury panel.

In the Cyberball (Williams et al., 2000) paradigm, participants take part in a virtual game of ball tossing with two other players, which are computer simulated unbeknownst to the participant. After 10 throws in which all players partake in the game equally, the participant is ostracized from the game by being excluded from further ball tosses. Contrary to the paradigms most other paradigms in this analysis, Cyberball does not include a variable of explicit social judgement. However, as ostracism threatens fundamental social needs like self-esteem and control through implicit negative feedback (Williams, 1997), it is perceived as distressful (Williams and Sommer, 1997). Since another meta-analysis (Kogler et al., 2015b) on a similar topic has included studies using the Cyberball paradigm, we decided to include these studies as well.

2.2. Literature search

Literature search was conducted between January of 2019 and January of 2020 according to PRISMA guidelines (Moher et al., 2009) using web of science (https://apps.webofknowledge.com/), Pubmed (https://www.ncbi.nlm.nih.gov/pubmed/) and google scholar (https://scholar.google.de/). Search terms contained 'STRESS' and 'fMRI' or 'IMAGING' and separate searches were conducted using the individual stress induction paradigms (Aversive Viewing Paradigm, Montreal Imaging Stress Test, imaging Maastricht Acute Stress Test, ScanSTRESS, Social-Evaluative Threat, Cyberball). Further, reference lists of related articles were scanned for additional publications on the topic. Studies

using physical stress induction like exercise or pain were excluded. After removal of duplicates, all abstracts were screened for suitability. Publications were included if they report on the cerebral response to acute stress induction via psychosocial stressors in healthy adult subjects. The resulting papers were checked for eligibility (see Fig. 1). Further, studies were excluded if no fMRI Data was collected, no stress induction was performed in the scanner, samples were used in several studies or the sample consisted of a patient population. If a sample was used in multiple studies, only the study initially reporting whole brain contrasts was included. In total, 35 studies were used in the systematic review as we only included studies using the MIST, ScanSTRESS, Cyberball, SET and AVP (see Table 1). To focus on whole brain data, region of interest studies were excluded. Studies were screened for all reported regions of activation, which were subsequently examined for overlap between the paradigms.

Literature search for the ALE Meta-analysis was performed following the same criteria that were used for systematic review. Publications were included if they report on the cerebral response to acute stress induction via psychosocial stressors in healthy adult subjects. The resulting papers were checked for eligibility (see Fig. 2). Further, studies were excluded if no fMRI data was collected, no stress induction was

performed in the scanner, sample were used in several studies or the sample consisted of a patient population. If no MNI coordinates for activation patterns were given in the text, corresponding authors were contacted. If they provided coordinates, the study was included. If not, it was excluded. In accordance with the ALE standards, region of interest analysis were also excluded (Müller et al., 2018). In total, 31 studies were used in further analysis (see Table 2). Please note that studies used in the systematic review and the ALE Meta-analysis do not coincide completely with each other as not all studies reported area information or MNI-coordinated, respectively.

2.3. Activation likelihood estimation (ALE) analysis

For the ALE analysis, we used the gingerALE (http://www.brainmap.org/software.html) tool based on the revised ALE algorithm for coordinate-based meta-analysis of neuroimaging results (Eickhoff et al., 2012). This approach treats activation foci reported by different studies as 3D Gaussian spatial probability distributions centered at the given coordinates. From these probability distributions, the algorithm calculates modelled activation maps for each experiment which contain the probabilities for each voxel (Turkeltaub et al., 2012). In the next step,
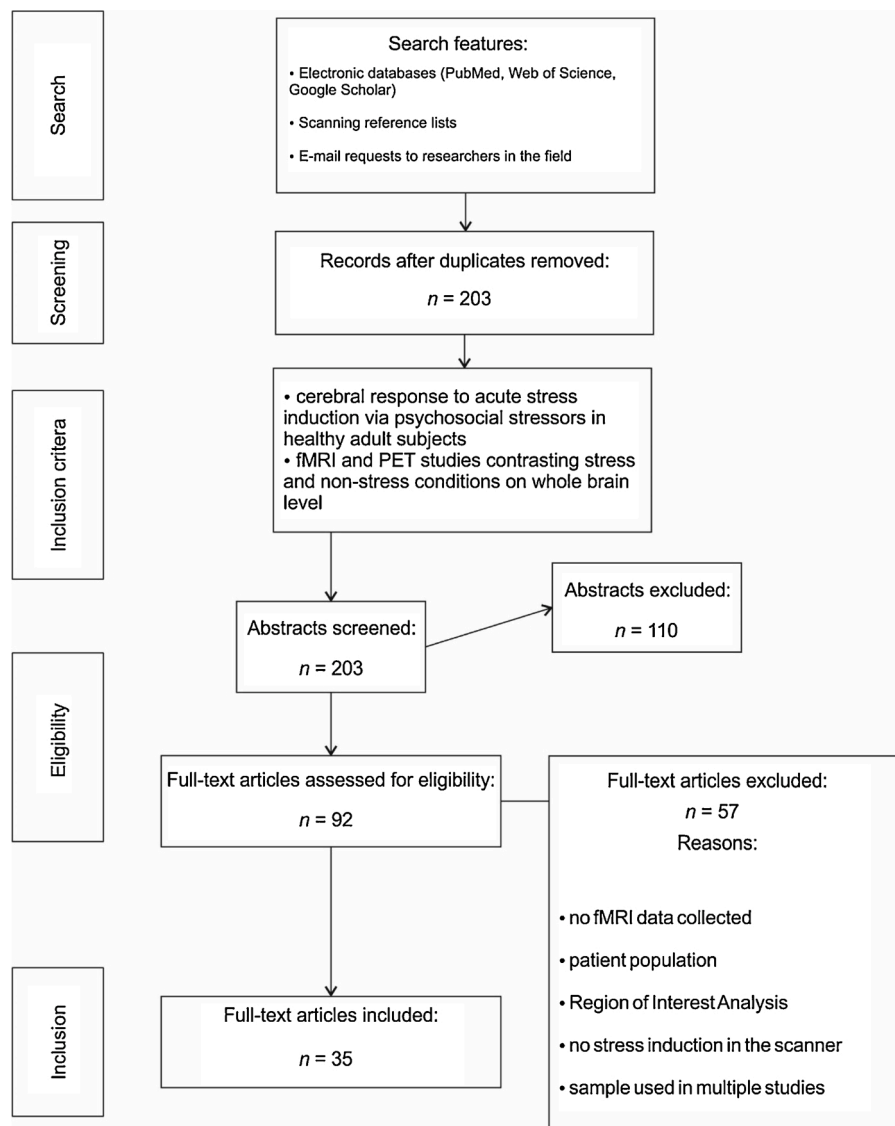

Fig. 1. PRISMA chart detailing literature search and inclusion criteria for the systematic review (Moher et al., 2009). Studies included in the systematic review do not coincide completely with studies included in the ALE as not all studies reported area information.

Table 1

Studies that were included in the systematic review. N gives the number of participants per study. Activation and deactivation refer to increases or decreases in brain activity after stress induction, respectively. The tasks include the aversive video paradigm (AVP), the Cyberball paradigm, the Montreal Imaging Stress Test (MIST), the ScanSTRESS paradigm and the Social Evaluative Threat (SET).

Study	N	Contrast	Task
Bolling et al. (2011)	23	Exclusion vs inclusion	Cyberball
Bolling et al. (2012)	20	Exclusion vs inclusion	Cyberball
Chung et al. (2016)	40	Stress vs control	MIST
Cousijn et al. (2010)	41	Stress vs control movie	AVP
Dahm et al. (2017)	86	Stress vs control	ScanSTRESS
Dedovic et al. (2005)	22	Stress vs control	MIST
Dedovic et al. (2009)	28	Control math and feedback from experimental stress math vs negative feedback	MIST
DeWall et al. (2012)	25	Exclusion vs inclusion	Cyberball
Elbau et al. (2018)	59	Task vs baseline	MIST
Everaerd et al. (2015)	118	Task vs baseline	AVP
Goodman et al. (2019)	26	Stress vs control	MIST
Gradin et al. (2012)	20	Activations with increasing social exclusion	Cyberball
Henckens et al. (2009)	18	Stress vs control movie	AVP
Henckens et al. (2016)	120	Stress vs control movie	AVP
Hermans et al. (2011)	80	Stress vs control movie	AVP
Hughes and Beer (2013)	18	Threat vs no-threat	SET
Kawamoto et al. (2012)	22	Exclusion vs inclusion	Cyberball
Kogler et al. (2017)	40	Stress vs control	MIST
Lederbogen et al. (2011)	32	Stress vs control	MIST/ ScanSTRESS
Lelieveld et al. (2013)	57	Exclusion vs inclusion	Cyberball
Masten et al. (2011)	18	Exclusion vs inclusion	Cyberball
Maurage et al. (2012)	22	Exclusion vs inclusion	Cyberball
Onoda et al. (2009)	26	Exclusion vs inclusion	Cyberball
Ossewaarde et al. (2010)	28	Stress vs control movie	AVP
Ossewaarde et al. (2011)	27	Stress vs control movie	AVP
Qin et al. (2012)	27	Stress vs control movie (group difference)	AVP
Qin et al. (2009)	20	Stress vs control movie	AVP
Radke et al. (2018)	80	Exclusion vs inclusion	Cyberball
Soliman et al. (2011)	40	Stress vs control	MIST
Streit et al. (2014)	42	Stress vs control	ScanSTRESS
Van Marle et al. (2009)	29	Stress vs control movie (group difference)	AVP
Wager et al. (2009a), 2009b	24	Threat vs no-threat	SET
Wager et al. (2009a), 2009b	18	Threat vs no-threat	SET
Wheelock et al. (2016)	53	Stress vs control	MIST
Zschucke et al. (2015)	36	Stress vs control	MIST

ALE scores are calculated by combining the modelled activation maps across experiments and are then compared to a null distribution that assumes spatial independence across experiments. The algorithm considers the different sample sizes as influence on reliability of the approximation true activation patterns by sizing of the Gaussian kernel size (Eickhoff et al., 2009). The null-distribution is derived by sampling of the modelled activation map for each study at random, which allows the null-distribution to reflect the probability of obtaining each ALE score trough random combination of the modelled activation maps.

The resulting non-parametric *p*-values were then thresholded at a cluster-level family-wise error (FWE) corrected threshold of p < .05 (cluster-forming threshold at voxel-level p < 0.001). We calculated an analysis for all paradigms combined ($N_{overall}$ = 1279; number of studies = 31; N_{AVP} = 451, Number of studies = 9; $N_{Cyberball}$ = 269, Number of studies = 8; $N_{ScanSTRESS}$ = 128, Number of studies = 2; N_{MIST} = 371; Number of Studies = 9; N_{SET} = 60, Number of studies = 3). We also calculated a separate analysis for all classical stress induction paradigm to see, if the Cyberball paradigm significantly changed the resulting clusters, as this paradigm does not entail a social judgment component.

3. Results

3.1. Systematic review

You can see supplementary Table 1 for a complete list containing all studies and the respective activations and deactivations in response to stress induction.

3.1.1. Cyberball
Increases in activation associated with the Cyberball paradigm have been repeatedly shown in the insula (Bolling et al., 2011; DeWall et al., 2012; Kawamoto et al., 2012; Lelieveld et al., 2013; Masten et al., 2011; Maurage et al., 2012; Onoda et al., 2009) while only one study found a deactivation (Bolling et al., 2012). Many of these studies also found increased activation in the middle and superior frontal gyrus (Bolling et al., 2011; DeWall et al., 2012; Masten et al., 2011; Maurage et al., 2012; Radke et al., 2018) while others found deactivation or conflicting results (Bolling et al., 2012; Gradin et al., 2012; Kawamoto et al., 2012). Moreover, social ostracism compared to inclusion in Cyberball is linked to changes in activity in the cerebellum (Bolling et al., 2011, 2012; DeWall et al., 2012; Masten et al., 2011), subcortical structures like the basal ganglia (Bolling et al., 2012; DeWall et al., 2012; Kawamoto et al., 2012) and motor and pre-motor areas (Bolling et al., 2011, 2012).

3.1.2. AVP
Activation patterns in studies using the AVP were highly diverse with little overlap between studies. Some report a stress related increase in activation in the amygdala and insula (Cousijn et al., 2010; Hermans et al., 2011; Qin et al., 2012; Van Marle et al., 2009). These regions are predominantly associated with salience processing and visuospatial attention. Moreover, activation was found in frontal and prefrontal regions (Hermans et al., 2011; Qin et al., 2009).

The only decrease in activation during stress induction was reported in the fusiform gyrus (Hermans et al., 2011). In contrast, other studies found an activation in this region (Henckens et al., 2009; Van Marle et al., 2009).

The AVP was the only paradigm in our analysis for which some individual studies did not report any significant changes in response to stress (Everaerd et al., 2015; Henckens et al., 2016; Ossewaarde et al., 2010, 2011).

3.1.3. SET
Similarly to the AVP, studies utilizing the SET report changes activation in the insula and amygdala that was however not uniform in its direction. While Hughes and Beer (2013) found only activation, Wager et al. (2009a), 2009b found either deactivations or conflicting patterns.
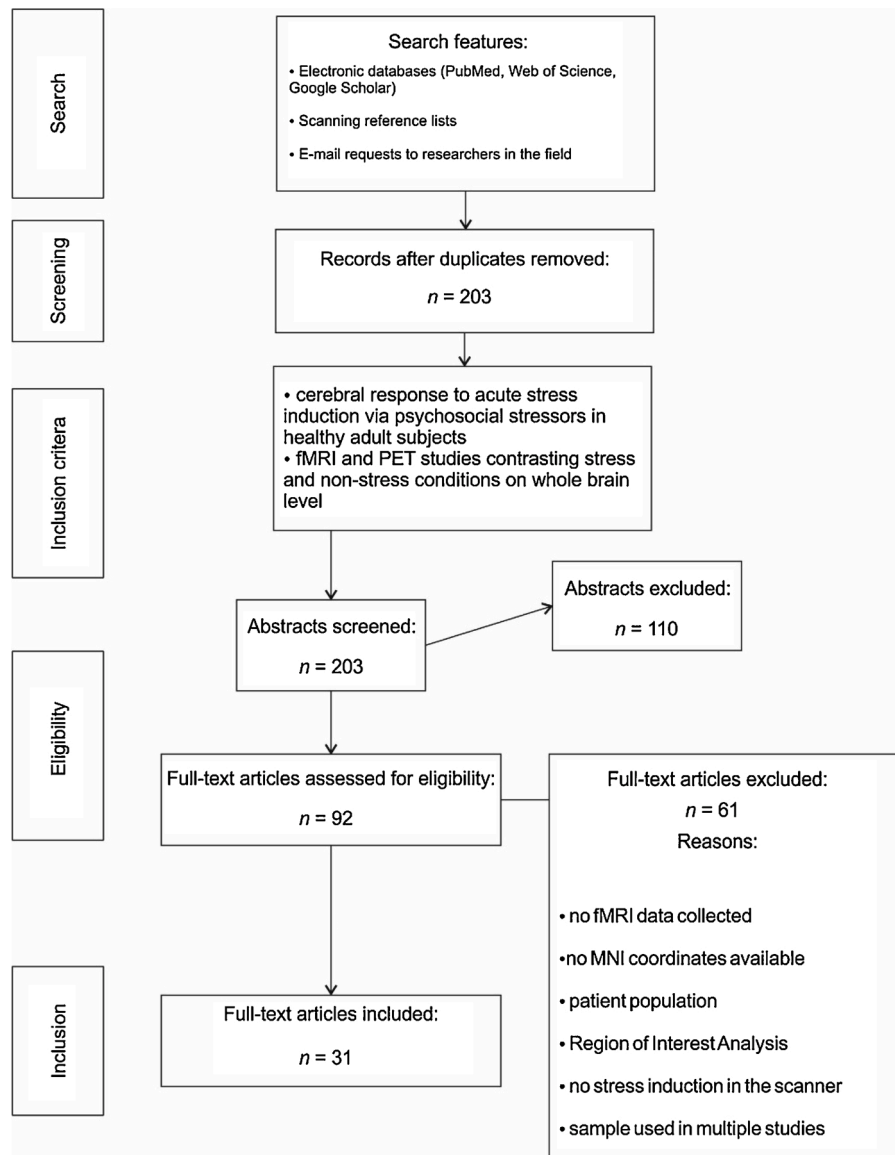
Fig. 2. PRISMA chart detailing literature search and inclusion criteria for the ALE meta-analysis (Moher et al., 2009). Studies included in the systematic review do not coincide completely with studies included in the ALE as not all studies reported area information or MNI coordinates.

Furthermore, all studies found changes in activation in the prefrontal cortex, again demonstrating increases (Hughes and Beer, 2013) and decreases (Wager, van Ast et al., 2009; Wager, Waugh et al., 2009).

3.1.4. MIST

Relative to the other paradigms, changes in activity in the amygdala and insula were less prevalent in the MIST (Dedovic et al., 2009; Kogler et al. (2015a); Lederbogen et al., 2011; Soliman et al., 2011; Wheelock et al., 2016; Zschucke et al., 2015). Activation patterns in frontal regions encompassed increases (Chung et al., 2016; Dedovic et al., 2009; Goodman et al., 2018; Kogler et al., 2017; Soliman et al., 2011; Wheelock et al., 2016; Zschucke et al., 2015) as well as decreases (Dedovic et al., 2009; Elbau et al., 2018; Goodman et al., 2018; Kogler et al., 2017; Soliman et al., 2011; Zschucke et al., 2015). These patterns were especially pronounced in the medial and inferior frontal gyrus as well as the lateral prefrontal cortex. Moreover, some studies showed activation in subcortical regions like the thalamus and basal ganglia (Dedovic et al., 2005; Lederbogen et al., 2011; Wheelock et al., 2016) while others showed divergent activation patterns (Dedovic et al., 2009; Soliman et al., 2011; Zschucke et al., 2015). Lastly, activation in motor

related areas like the precentral gyrus and cerebellum have been detected (Dedovic et al., 2005; Elbau et al., 2018; Kogler et al., 2017; Wheelock et al., 2016).

3.1.5. ScanSTRESS

Between the two studies using the ScanSTRESS paradigm, there is little overlap in activation patterns. Only increases in activation in the insula were consistent between both studies (Dahm et al., 2017; Streit et al., 2014).

3.2. Activation likelihood estimation (ALE) analyses

As explained above, we performed two separate ALE analyses, one including data from all stress induction paradigms used in the MRI scanner and one excluding data obtained with the Cyberball paradigm, but including data obtained with all other paradigms.

3.2.1. ALE analysis of all stress induction paradigms

3.2.1.1. Activation. The analysis across all stress induction paradigms

Table 2

Studies that were included in the Activation likelihood estimation (ALE) analysis. N *gives the number of participants per study. The tasks include the aversive video paradigm (AVP), the Cyberball paradigm, the Montreal Imaging Stress Test (MIST), the ScanSTRESS paradigm and the Social Evaluative Threat (SET).*

Study	N	Contrast	Task
Everaerd et al. (2015)	118	Task vs baseline	AVP
Henckens et al. (2009)	18	Stress vs control movie	AVP
Henckens et al. (2016)	120	Stress vs control movie	AVP
Hermans et al. (2011)	80	Stress vs control movie	AVP
Ossewaarde et al. (2010)	28	Stress vs control movie	AVP
Ossewaarde et al. (2011)	27	Stress vs control movie	AVP
Qin et al. (2012)	20	Stress vs control movie	AVP
Qin et al. (2009)	27	Stress vs control movie (group difference)	AVP
Van Marle et al. (2009)	13	Stress vs control movie (group difference)	AVP
Bolling et al. (2012)	20	Exclusion vs inclusion	Cyberball
Bolling et al. (2011)	23	Exclusion vs inclusion	Cyberball
DeWall et al. (2012)	25	Exclusion vs inclusion	Cyberball
Gradin et al. (2012)	20	Activations with increasing social exclusion	Cyberball
Masten et al. (2011)	18	Exclusion vs inclusion	Cyberball
Onoda et al. (2009)	26	Exclusion vs inclusion	Cyberball
Radke et al. (2018)	80	Exclusion vs inclusion	Cyberball
Lelieveld et al. (2013)	57	Exclusion vs inclusion	Cyberball
Chung et al. (2016)	40	Stress vs control	MIST
Dedovic et al. (2009)	28	Control math and feedback from experimental stress math vs negative feedback	MIST
Elbau et al. (2018)	59	Task vs baseline	MIST
Kogler et al. (2015a), 2015b	43	Nonregulation Stress vs control	MIST
Kogler et al. (2017)	40	Stress vs control	MIST
Soliman et al. (2011)	40	Stress vs control	MIST
Wheelock et al. (2016)	53	Stress vs control	MIST
Zschucke et al. (2015)	36	Stress vs control	MIST
Lederbogen et al. (2011)	32	Stress vs control	MIST
Dahm et al. (2017)	86	Stress vs control	ScanSTRESS
Streit et al. (2014)	42	Stress vs control	ScanSTRESS
Hughes and Beer (2013)	18	Threat vs no-threat	SET
Wager et al. (2009a), 2009b	24	Threat vs no-threat	SET
Wager et al. (2009a), 2009b	18	Threat vs no-threat	SET

(n = 31 studies) revealed two significant clusters of convergent activity extending to the bilateral insula, bilateral claustrum and the inferior frontal gyrus (Cluster 1: k = 2104, z = 5.14; Cluster 2: k = 1776, z = 6.29; Cluster 3: k = 808, z = 5.33; see Table 3 Fig. 3).

3.2.1.2. Deactivation. The analysis across all stress induction paradigms revealed one significant cluster of convergent deactivation extending parahippocampal gyrus including the amygdala in the right hemisphere

(k = 976, z = 6.44; see Table 3).

3.2.2. ALE analysis without Cyberball paradigm

3.2.2.1. Activation. The analysis across stress induction paradigms (n = 23 studies) excluding the Cyberball paradigm revealed five significant clusters of convergent activity. The first two clusters extended to the bilateral insula and bilateral claustrum (Cluster 1: k = 1464, z = 6.45; Cluster 2: k = 100, z = 4.80; see Table 4). The third cluster encompassed the right lentiform nucleus and thalamus (Cluster 3: k = 920, z = 5.53). The fourth cluster contained the precentral gyrus and insula (Cluster 4: k = 840, z = 4.69) and the fifth cluster contained the inferior and middle temporal gyrus as well as the middle occipital gyrus (Cluster 5: k = 808, z = 4.44).

3.2.2.2. Deactivation. The analysis across stress induction paradigms excluding the Cyberball paradigm revealed three significant clusters of convergent deactivations. The first cluster contained the Parahippocampal gyrus (Cluster 1: k = 984, z = 6.58; see Table 4, Fig. 4). The second cluster comprised precuneus and cingulate gyrus (Cluster 2: k = 608, z = 3.88). The third cluster extended from the superior temporal gyrus to the precentral gyrus (Cluster 3: k = 552, z = 4.54).

4. Discussion

In the present study, we performed a meta-analysis of BOLD activation and deactivation patterns across different acute stress induction paradigms using the activation-likelihood estimation method (Eickhoff et al., 2009, 2012; Turkeltaub et al., 2012). The aims of the present study were (1) to identify convergent patterns in brain activity during psychological stress and (2) to identify differences between different psychological stress induction paradigms.

The ALE revealed two activation clusters including the insula, the claustrum, and the inferior frontal gyrus in both hemispheres across all paradigms. The function of the insula is multifaceted, playing a role in somatic and pain perception, interoception and social cognition (Uddin et al., 2017). As part of the salience network (Seeley et al., 2007), the insula is proposed to integrate external sensory and internal emotional information and activate central executive networks (Uddin, 2015). The insula has been described as part of the paralimbic or limbic integration cortex (Augustine, 1996). As such, it has connections to other parts of the limbic system like the amygdala and the hippocampus which are strongly integrated in the regulation of the HPA axis (Ulrich-Lai and Herman, 2009).

Corresponding to the analysis by Kogler et al. (2015b), we found activation of the insula and inferior frontal gyrus across all stress paradigms. This indicates that these structures are not only relevant in the processing of physiological stressors like pain but also play a critical role for the evaluation and reaction to social stress. Structural changes in the amygdala have been shown to correlate with mindfulness and stress regulation (Hölzel et al., 2010). Furthermore, corticotrophin-releasing factor is released in the amygdala during stressful events (Gray and Bingaman, 1996) indicating that amygdala activation is modulated by the stress response. In animal studies, it could also be demonstrated that prolonged behavioral stress enhances synaptic connectivity in the basolateral amygdala (Vyas et al., 2006). Moreover, the amygdala has been suggested to play a central role in the activation pathway of the HPA axis (Ulrich-Lai and Herman, 2009). Here, the medial amygdala mediates the influence of psychological stress (Herman et al., 2005). Contrary to the amygdala, the insula has not been in the central focus of stress research. However, there is evidence that the insula is associated with differences in activation in response to stress between individuals with low and high early life stress (Mothersill and Donohoe, 2016). This indicates that these structures play a part in the vulnerability to the influence of acute stress. Our results provide further support that both

Table 3

Brain regions and MNI coordinates for peaks showing convergence in activation for stress induction for all paradigms combined.

Paradigm	Contrast	Cluster	Macroanatomical location	Cytoarchitectonic location	X	Y	Z	Z value
All paradigms	Activation	Cluste 1 (k = 2104)	Insula	BA 13	36	22	0	5.14
			Claustrum	BA 47				
			Extra-Nuclear					
		Cluster 2 (k = 1776)	Insula	BA 13	−32	20	4	6.29
			Claustrum	BA 47				
			Inferior Frontal Gyrus	BA 45				
			Extra-Nuclear					
		Cluster 3 (k = 808)	Lentiform nucleus	Globus pallidus	14	0	−2	5.33
			Thalamus	Anterior nucleus				
				Amygdala				
	Deactivation all paradigms	Cluster 1 (k = 960)	Parahippocampal Gyrus	BA 34	18	−6	−18	6.44
				BA 28				
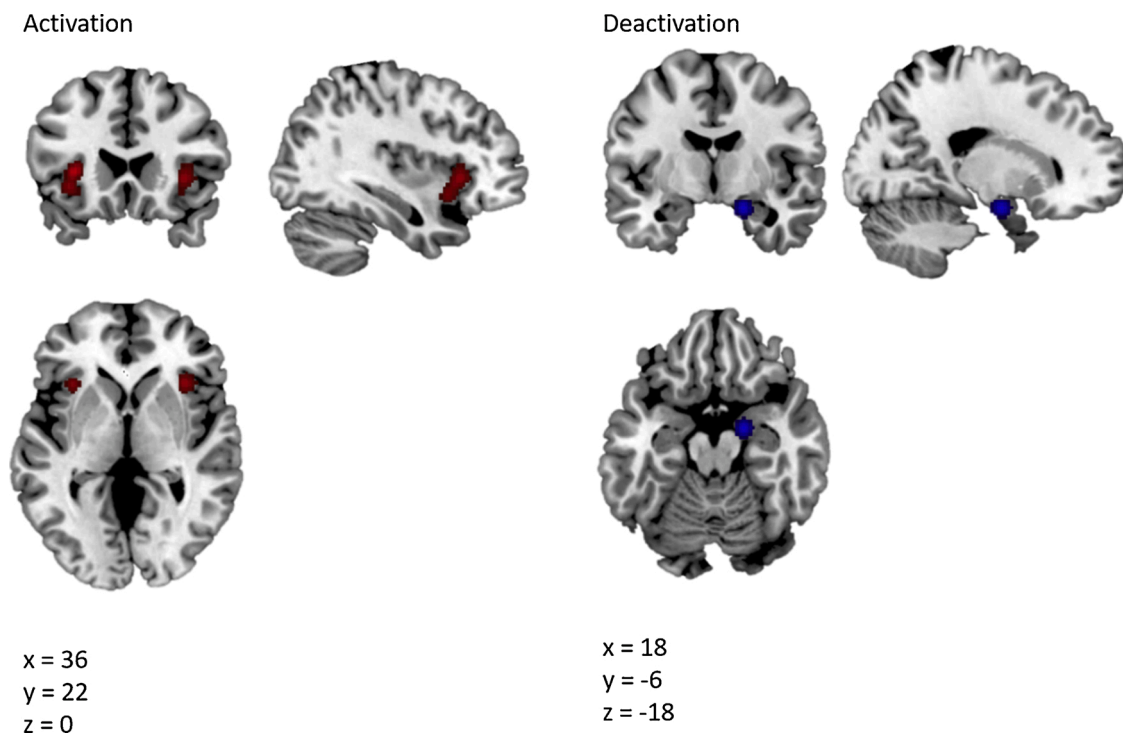
Fig. 3. ALE map of clusters of activation (red) and deactivation (blue) across all stress induction paradigms.

the amygdala and the insula are functionally involved in the psychosocial stress response.

The claustrum, which is a thin layer of gray matter adjacent to the insula, acts as an integration hub for information across different modalities (Crick and Koch, 2005). The structure has also been implicated in consciousness (Koubeissi et al., 2014; Yin et al., 2016). This indicates that during stress the brain shows activation in areas associated with interoception and pain processing suggesting that the attention of the participants is focused inward on internal emotional processes. The inferior frontal gyrus on the other hand has been associated with semantic and phonological processing as well as working memory and fine movement control (Liakakis et al., 2011). As most stress induction paradigms imply a taxing cognitive task, the activation of the inferior frontal gyrus could be due to task demands on cognitive capacities such as arithmetic calculation and mental rotation. Moreover, we found a significant deactivation across all paradigms in the right amygdala and parahippocampal gyrus. This result pattern is surprising as the amygdala has been associated with the processing of fearful stimuli (Adolphs et al., 2005; LeDoux, 2003), fear perception (Lindquist et al., 2012), and the subjective feeling of anxiety during stress (Wang et al., 2005). Lastly, the parahippocampal gyrus is part of the default mode network (DMN)

which is a brain system preferentially active when individuals are not focused on the external environment (Buckner et al., 2008). However, the relationship between acute stress and the DMN is not well understood. Patients suffering from posttraumatic stress disorder show decreases in the DMN (Koch et al., 2016). In response to acute stress, however, the DMN shows an increase in resting state activity termed alerted default mode (Clemens et al., 2017; van Oort et al., 2017). Studies using the MIST have consistently found amygdala activations at the onset of the stressor (Pruessner et al., 2004, 2008). It could be speculated that the amygdala is shortly activated as a salience detector but habituates quickly during the stress induction. Moreover, it could be hypothesized that the lower activation of the amygdala during stress induction arises from the participants trying to regulate their subjective feeling of fear to be more focused on the task at hand. Reappraisal, namely the reevaluation of the stressor and the available resources, has been associated with decreases in amygdala activation (Goldin et al., 2008) and regulation of negative affect (Urry et al., 2006). Here, cortisol has been associated with reducing emotion related activity (Jentsch et al., 2019).

In the analysis containing only the classical stress induction paradigms, there was an additional cluster comprising the lentiform nucleus.

Table 4
Brain regions and MNI coordinates for peaks showing convergence in activation for stress induction for standard paradigms combined.

Paradigm	Contrast	Cluster	Macroanatomical location	Cytoarchitectonic location	X	Y	Z	Z value
Standard paradigms	Activation	Cluste 1 (k = 1464)	Insula	BA 13				
			Claustrum	BA 47	−32	20	4	6.45
			Extra-Nuclear					
		Cluster 2 (k = 1000)	Insula	BA 13	34	24	2	4.80
			Claustrum					
			Lentiform Nucleus	Medial Globus Pallidus				
		Cluster 3 (k = 920)		Lateral Globus Pallidus	14	0	−2	5.53
			Thalamus	Ventral Anterior Nucleus				
		Cluster 4 (k = 840)	Precentral Gyrus	BA 44	52	6	4	4.69
			Insula	BA 13				
			Inferior Temporal Gyrus	BA 37				
		Cluster 5 (k = 808)	Middle Temporal Gyrus		44	−64	6	4.44
			Middle Occipital Gyrus	BA 19				
	Deactivation	Cluster 1 (k = 984)		Amygdala	18	−6	−18	6.58
			Parahippocampal Gyrus	BA 34				
				BA 28				
			Precuneus	BA 31				
		Cluster 2 (k = 608)	Cingulate Gyrus	BA 23	2	−50	30	3.88
			Posterior Cingulate	BA 30				
		Cluster 3 (k = 552)	Superior Temporal Gyrus	BA 22	−56	−2	2	4.54
			Precentral Gyrus	BA 6				

Activation

Deactivation

x = 13
y = 20
z = 3

x = 19
y = -4
z = -3
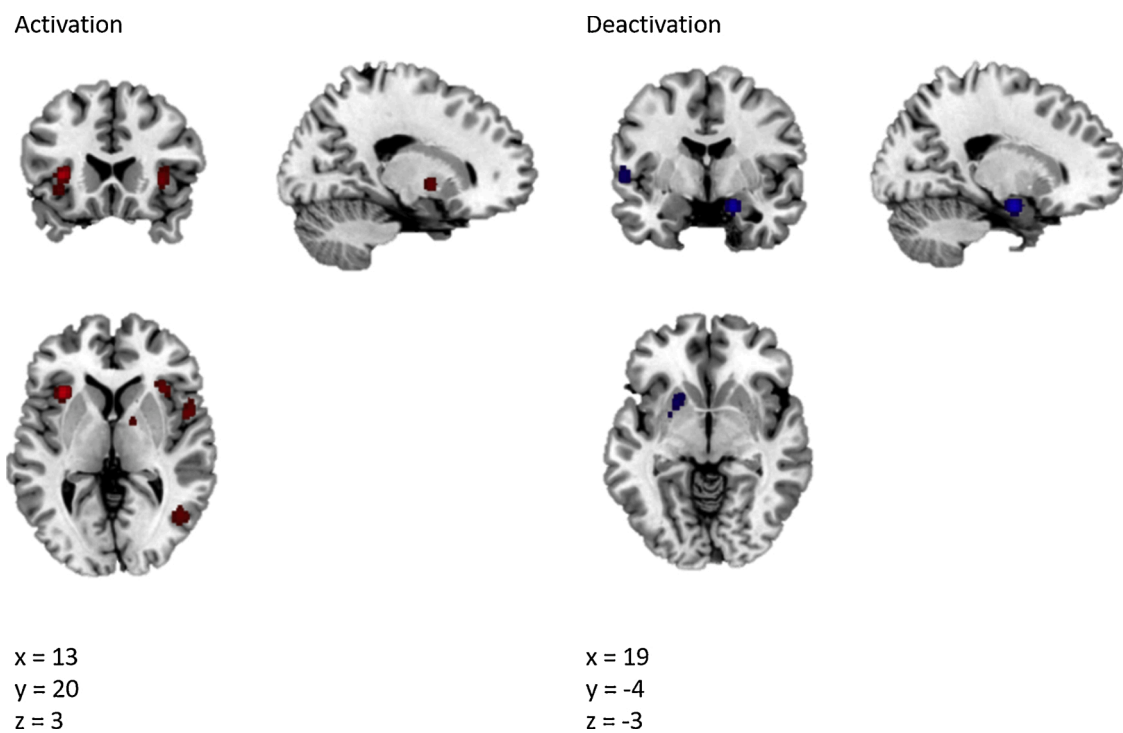
Fig. 4. ALE map of clusters of activation (red) and deactivation (blue) across all stress induction paradigms excluding the Cyberball paradigm.

The lentiform nucleus consists of the globus pallidus and the putamen. Both structures are involved in movement and motor preparation (Brotchie et al., 1991; Crutcher and DeLong, 1984; Postuma and Dagher, 2006). In the context of stress, the functional involvement of these structures is not clear. It could be speculated that acute stress leads to an increase general muscle tension and preparation for flight as part of the fight-or-flight response (Cannon, 1939). The inferior parietal lobule has been implicated in various functions. It has been proposed to play part in emotion perception (Engelen et al., 2015), but also in the processing of speech (Stoeckel et al., 2009). Thus, it could play a functional role in the stress response but also in the cognitive processing of the task presented.

Overall, we could found that different paradigms for psychological stress induction activate and deactivate similar brain structures. Analysis of activation patterns between the classical stress induction

paradigms resulted in more overlapping clusters across studies. This could indicate that the Cyberball paradigm represents an outlier in the here presented analysis of imaging stressors. This is supported by the fact that the Cyberball paradigm does not result in increased cortisol levels due a HPA axis activation (Helpman et al., 2017), in contrast to the other paradigms (e.g. Akdeniz et al., 2014; Henckens et al., 2009).

Due to the relatively small number of studies with each stress induction paradigm, it was not possible to perform separate analyses for the different paradigms. However, as there are substantial differences between all paradigms, it still is useful to look at possible differences in the neural response. In this regard, we performed a systematic review of the imaging stress literature to examine the associated activation patterns. Here, the Cyberball paradigm stood out as it demonstrated substantial activation in motor-related areas. In the context of stress, the

functional involvement of these structures related to movement control is not clear. As the Cyberball paradigm involves virtual ball tosses, activity in motor function related areas could be due imaginary movement. The angular gyrus, which was prominently activated in the MIST, has been suggested to be a cross-modal hub where converging multisensory information is processed (Seghier, 2013). As part of the inferior parietal lobule it has been proposed to play part in emotion perception (Engelen et al., 2015), but also in the processing of speech (Stoeckel et al., 2009). Thus, it could play a functional role in the stress response but also in the cognitive processing of the task presented. A further outlier presented itself in the AVP paradigm, as it was the only paradigm for which no differences between a stress and control condition could be found. Therefore, the AVP might be the least effective paradigm to induce stress-related activity changes in the scanner and should potentially be substituted by a stronger socially evaluative component.

In sum, activation patterns vary to some degree between the different stress induction paradigms. Even though many paradigms are associated with activation changes in medial and ventromedial prefrontal areas as well as limbic structures, it needs to be kept in mind that the precise loci of activation differ between the studies. If these variations are incidental or related to differences between the paradigms in terms of social evaluation, performance pressure and difficulty needs to be evaluated further.

5. Limitations

Overall, 31 papers were included in this ALE meta-analysis. This sample was adequate to reliably calculate overlaps between different stress induction paradigms. However, it would of course be important to conduct separate ALE analyses for the different paradigms. Unfortunately, the number of studies published for each paradigm is not high enough to reliably identify all relevant clusters (Eickhoff et al., 2016). Partly, this is due to the lack of studies with these paradigms. However, we have noticed during the literature research that many studies which would be eligible for our meta-analysis did not report on main effects of stress on BOLD changes. Unfortunately, not all corresponding authors answered our requests for data or had the necessary data available. Even if these contrasts might not be the central focus of the study, we would like to urge other researchers to still include these contrasts in their supplementary material or provide it on inquiry if possible. This would improve further research as more included studies would lead to better powered meta-analyses allowing for further contrast analysis.

The low number of studies might also explain why we were unable to find changes in activation in other expected brain areas. For example, we could not detect activity changes in the medial prefrontal cortex (mPFC) which has been demonstrated to be involved in the regulation of the stress response (Diorio et al., 1993; Radley et al., 2006). However, the lack of activation changes in the mPFC could also be due to the time course of the stress induction procedure as the mPFC regulates the duration and thus termination of the stress response. It could be thus speculated that the stress reaction is likely not yet terminated during the session, as the stressor is still present.

6. Conclusion

The current study investigated the influence of acute stress on changes in the BOLD signal. To this end, we analyzed brain activation patterns in response the most commonly used psychological stress induction paradigms. The analysis showed significant convergence in the insula, the claustrum, and the inferior frontal gyrus. This indicates that these structures play a central role in the stress response regardless of paradigm used.

To evaluate differences in activation patterns between the paradigms, we performed a systematic review of the literature. Although many studies show similar activation patterns in the prefrontal and temporal cortex with different paradigms, it should to be noticed that

precise loci of activation differ substantially between the studies.

Future research is needed to investigate further commonalities and differences between the different paradigms. Moreover, deactivation studies in animal models and studies with neurological patients could help to expand the knowledge of these structures in the context of the acute stress response.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2021.01.001.

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