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Functional topography of anger and aggression in the human cerebellum

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ABSTRACT

New insights into the functional neuroanatomic correlates of emotions point toward the involvement of the cerebellum in anger and aggression. To identify cerebellar regions commonly activated in tasks examining the experience of anger and threat as well as exerting an aggressive response, two coordinate-based activation likelihood estimation meta-analyses reporting a total of 57 cerebellar activation foci from 819 participants were performed. For anger processing (18 studies), results showed significant clusters in the bilateral posterior cerebellum, overlapping with results from previous meta-analyses on emotion processing, and implying functional connectivity to cognitive, limbic, and social canonic networks in the cerebral cortex. By contrast, active aggression expression (10 studies) was associated with significant clusters in more anterior regions of the cerebellum, overlapping with cerebellar somatosensory and motor regions and displaying functional connectivity with the somatomotor and default mode network. This study not only strengthens the notion that the cerebellum is involved in emotion processing, but also provides the first quantitative evidence for distinct cerebellar functional activation patterns related to anger and aggression.

1. Introduction

Anger is an intense emotional state which is triggered when an individual is frustrated, provoked, threatened, or otherwise subjected to aversive conditions. The strong activation of the sympathetic nervous system goes accompanied by hypervigilance, attentional narrowing, specific physical displays (e.g., facial expressions and body posture), as well as distinct linguistic expressions related to heat and pressure build-up (Alia-Klein et al., 2020). While anger can promote intrinsic motivation, effortful goal-directed behaviors and competitiveness (Panksepp and Zellner, 2004), the strong approach-related motivational tendencies underlying anger can culminate into aggressive behavior as a means to eliminate an unwanted situation in order to reach a desired state of affairs (Berkowitz and Harmon-Jones, 2004; Stein and Levine, 1989). Neuroscientific evidence has shown that the internally experienced approach motivation linked to anger originates from the instinctual action system located in the subcortical parts of the mammalian brain (Panksepp and Biven, 2012). Specifically, the amygdala, hypothalamus and periaqueductal gray of the midbrain comprise the subcortical circuit that drives anger and aggression. The amygdala directly signals the hypothalamus when a potential threat is being perceived, whereas the hypothalamus is central to the regulation of the autonomic system and has a gain function to prepare the body for fight-flight behaviors. From there, fibers run to the periaqueductal gray of the midbrain, which, in the present context, activates the fight mode (Mobbs et al., 2007), potentially initiating (defensive) aggressive behavior (Blair, 2012, 2001), as has been shown in cats and rodents (Siegel et al., 1999). This subcortical circuit together with the dorsal anterior cingulate cortex and insula is part of the brain's salience network dedicated to detecting behaviorally-relevant salient changes in internal states following external sensory input (Seeley et al., 2007). Arguably, high levels of arousal and stress reactivity in combination with uncontrollable situations sensitize this subcortical anger circuit and fuel defensive/offensive (reactive) aggressive behavior. In addition, the frontal and temporoparietal cortex are part of the brain's default mode network and involved in self-referential processing, mentalizing and emotion regulation (Alia-Klein et al., 2020; Fox et al., 2005; Van Overwalle and Baetens, 2009). The executive control network that is made up of the anterior cingulate, dorsolateral and ventromedial parts of the prefrontal cortex contributes to neural processes associated with the conscious experience of anger and top-down regulation of the subcortical anger circuit (Schwabe et al., 2010). Indeed, the cortico-limbic centered network models provide an empirically based neuroanatomic framework for understanding the neural correlates of anger and aggression. However, despite the growing body of evidence, a brain structure which is not typically considered in anger and aggression is the cerebellum (Adamaszek et al., 2017).

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In addition to its contributions to the functionality of the three intrinsic connectivity networks mentioned earlier (Habas et al., 2009), further evidence pointing towards involvement of the cerebellum in anger and aggression stems from neuropsychological studies that found a relation between cerebellar damage and emotion (dys)regulation. In particular, lesions confined to the vermis have been associated with increased impulsivity and aggressive behavior in humans (Hoche et al., 2018; Schmahmann, 2000; Schmahmann et al., 2007), but tamed behavior in cats, squirrels and rhesus monkeys (Berman et al., 1974; Peters and Monjan, 1971). Furthermore, subdural electric stimulation of the vermis has proven effective in ameliorating uncontrollable aggressive behavior in a variety of psychiatric patients (Heath et al., 1980, 1978). In a recent study, optogenetic stimulation was used to modulate activity of the vermis of lobule VII in rats to show that inhibiting Purkinje cell activity increased the frequency of attacks towards an intruder. Conversely, the opposite behavioral pattern was observed when Purkinje cell activity in these rats was increased (Jackman et al., 2020). These findings are in line with previous results showing that electric stimulation of the fastigial nucleus induces sham rage in cats (Zanchetti and Zoccolini, 1954). As Purkinje cells in the vermis tonically inhibit the fastigial nucleus of the deep cerebellar nuclei, electrically stimulating the fastigial nucleus directly or indirectly by releasing Purkinje cell-mediated inhibition can induce aggressive behavior. Similarly, stimulating the anterior cerebellar cortex after electric stimulation of the hypothalamus causes a reduction of the initially observed visceral responses (Lisander and Martner, 1971). This suggests that efferent inhibitory connections between Purkinje cells in the cerebellar cortex and deep cerebellar nuclei result in a dampening of otherwise strong autonomic responses.

The lesion and intracranial stimulation studies concur with the growing number of functional neuroimaging studies that demonstrate distinct cerebellum activation in response to non-motor related aspects of emotions (Adamaszek et al., 2017; Guell et al., 2018; King et al., 2019; Stoodley and Schmahmann, 2010, 2009). Arguably owing to its reciprocal connections to cortico-limbic circuits (Allen et al., 2005; Habas et al., 2009; Leggio and Olivito, 2018; Middleton and Strick, 2001), the cerebellum is proposed to integrate bodily and external sensory signals required for the processing of threat-related stimuli to facilitate the transition from perception to action.

Although meta-analytic results from functional neuroimaging studies have confirmed activation of the cerebellum during emotion processing (E et al., 2014; Stoodley and Schmahmann, 2009), cerebellar activation patterns specifically related to anger processing and aggression remain unknown. To address this issue, we conducted a systematic literature search for functional neuroimaging studies employing anger processing tasks and studies that used anger and aggression induction paradigms, and performed an activation likelihood (ALE) meta-analysis to identify anger- and aggression-related activation patterns in the cerebellum.

2. Methods

2.1. Literature search and data acquisition

To identify eligible studies, the PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://apps.webofknowledge.com/) databases were searched with three different types of query: (1) aggression induction-specific studies (searching for “anger” or “aggression” in combination with “fMRI”); (2) emotional face processing-specific (searching for “angry faces” in combination with “fMRI”); (3) cognitive-emotional-specific (search for “emotional Stroop”, “emotional go/no-go”, “emotional stop signal”, or “emotional n-back” in combination with “fMRI”). Additionally, the studies contained within a recent ALE meta-analysis on aggression (Wong et al., 2019) as well as the results from a query using the keywords “anger” and “aggression” on NeuroQuery (https://neuroquery.org/) were included in the initial record list. After duplicate removal and a title scan of the obtained records, which removed studies that were obviously not related to the research question (e.g., animal research, cancer treatment), the full-texts of the remaining 412 studies were screened for suitability. Only English-language studies in peer-reviewed journals and involving participants of 18 years or older were included. Further, studies were included if they reported an fMRI experiment including an anger- or aggression-specific contrast reported as a main effect with significant hemodynamic activation in the cerebellum. That is, although we restricted our search to whole-brain analyses (Müller et al., 2018), we subsequently treated the cerebellum as a region of interest (ROI) and only extracted coordinates from this circumscribed region. Note that this approach is different from previous ALE meta-analyses focusing on the cerebellum (E et al., 2014; Stoodley and Schmahmann, 2009). Typically, the database queries already include a term referring to the cerebellum, limiting the results to studies which specifically focus on cerebellar activation. However, cerebellar activation is frequently not explicitly mentioned in the title, abstract or main body of the text and is merely referred to in the supplementary materials. Thus, by adopting a strategy which first scanned a large number of “cerebellar non-specific” studies and subsequently limiting the search on cerebellar activation points, we were able to identify studies that would not have been discovered if we had included “cerebell*” in the literature search queries.

Fig. 1 illustrates the study selection procedure. The lack of either an anger- or aggression-specific contrast or significant cerebellar activation, as well as exclusive reporting of ROI analyses (predominantly from the amygdala and fronto-cingulate regions) were the main reasons for exclusion. The final sample included 28 studies, which we subsequently divided into two groups: The “passive condition” comprised studies which involved the processing and/or experience of experimentally induced anger and threat (primarily through face processing tasks), while studies in the “active condition” employed experimental paradigms eliciting overt aggressive behavior (primarily variants of the Taylor aggression paradigm). Table 1 provides an overview of the included studies. Of the 90 studies that were excluded because no significant cerebellar activation was reported, 10 could be classified as active and 80 as passive. This illustrates the relative scarcity of fMRI studies employing explicit aggression induction paradigms, but also suggests that cerebellar activation is significantly more likely in active compared to passive anger and aggression scenarios ($X^2(1) = 14.63$, $p < .001$).

2.2. Activation likelihood estimation

Activation likelihood estimation is a method to estimate convergent activation patterns across studies while accounting for spatial uncertainty and differences in sample size (Eickhoff et al., 2009). In particular, individual activation peaks are modelled as three-dimensional probability distributions, combined in a modelled activation map, and tested against a spatial null distribution. Initially, significant clusters were determined in 10,000 permutations with a cluster forming threshold of $p < .001$ and a cluster-level family-wise error threshold of $p < .05$. Additionally, taking into account the relatively small number of studies, we ran the same analyses with a more lenient cluster forming threshold of $p < .01$. All analyses were performed on MNI coordinates using NiMARE (version 0.0.3; https://github.com/neurostuff/NiMARE). Talairach coordinates were transformed into MNI space using the Lancaster transform *icbm2tal* (Laird et al., 2010; Lancaster et al., 2007). Since the analyses were restricted to cerebellar coordinates, we created a mask corresponding to the cerebellum as defined in the MNI structural atlas (Collins et al., 1995; Mazziotta et al., 2001) in FSL (Smith et al., 2004). This mask was the null space in all analyses (as opposed to the whole brain), allowing for a region of interest-specific analysis of reported activation peaks.

To visualize clusters, we overlaid the ALE results onto a standard MNI template (Colin27_T1_seg_MNI; www.brainmap.org/ale/Colin27_T1_seg_MNI.nii.gz) in Mango (version 4.1; http://ric.uthscsa.edu/mango/). Additionally, the results were

Table 1
Overview of studies included in the meta-analysis.

Study	Population	*N* (f)	Age (*M* ± *SD*)	Task	Stimuli	Included contrast (number of coordinates)	Reference space
Active condition							
Brunnlieb, Münte, Krämer, Tempelmann, & Heldmann (2013)	HC (placebo and vasopressin administration between participants)	36 (0); 15 included in placebo condition	25.0 ± 4.0 [26.5 ± 4.3]	Taylor Aggression Paradigm	Provocation: aversive sound	Stronger activation in left cerebellum during active relative to passive trials for participants with placebo administration (4)	MNI
Buades-Rotger, Beyer, & Krämer (2017)	HC	36 (36); 27 in analysis of included contrast	22.0 ± 4.0	Fight-or-escape paradigm (adaption of Taylor Aggression Paradigm)	Provocation: aversive sound	Stronger activation in right cerebellum in fight relative to avoid decisions (2)	MNI
Chester & DeWall (2016)	HC	69 (47)	18.7 ± 0.9	Taylor Aggression Paradigm	Provocation: aversive sound	Stronger activation during retaliation to non-retaliation in right cerebellum with individual retaliatory aggression as regressor (1)	MNI
Dambacher et al. (2015)	HC	15 (0)	22.3 ± 2.4	Taylor Aggression Paradigm	Provocation: aversive sound	Stronger activation in right cerebellum during provocation relative to no provocation (2)	TAL
Emmerling et al. (2016)	HC	15 (0)	22.3 ± 2.4	Taylor Aggression Paradigm	Provocation: aversive sound	Stronger activation in right cerebellum during retaliation to provoking opponent relative to non-retaliation to non-provoking opponent (1)	TAL
Gan et al. (2016)	Clinically relevant IED and HC	9 (0) and 9 (0)	34.4 ± 7.5 and 31.8 ± 6.5	Point subtraction task	Earning money (reward) or making opponent lose money (retaliation)	Across both groups, stronger activation in left cerebellum when choosing retaliation over reward (1)	MNI
Krämer, Jansma, Tempelmann, & Münte (2007)	HC	20 (11), 15 included in analysis	22.9 ± 2.2	Taylor Aggression Paradigm	Provocation: aversive sound	Stronger activation in left cerebellum during high relative to low provocation in decision phase (1)	TAL
Repple et al. (2018)	HC (male and female)	42 (20)	24.8 ± 2.8 and 27.5 ± 9.3	Taylor Aggression Paradigm	Provocation: Making opponent lose points	Across males and females, stronger activation in right cerebellum in case of high relative to low provocation in feedback phase (1)	MNI
Wagels et al. (2019)	HC (testosterone and placebo administration within participants)	105 (0); 93 in final sample	24.2 ± 3.8	Taylor Aggression Paradigm	Provocation: Making opponent lose money	Across testosterone and placebo conditions, stronger activation in left cerebellum in case of high relative to low provocation during feedback phase (3)	MNI
White, Brislin, Sinclair, & Blair (2014)	HC	21 (9)	28.1 ± 8.1	Social unfairness game (adaptation of Taylor Aggression Paradigm)	Punishment: spending own money to make opponent lose money	With higher punishment of opponent, higher activation of bilateral cerebellum and lower activation of left culmen (4)	MNI
Passive condition							
Aupperle et al. (2012)	HC (two doses of pregabalin and placebo administration within participants)	16 (6)	23.2 ± 2.6	Emotional face matching task	Colored photographs of faces	Across drug and placebo conditions, weaker activation in right cerebellum in response to angry relative to happy faces (1)	TAL
Bedi, Phan, Angstadt, & De Wit (2009)	HC (two doses of MDMA and placebo administration within participants)	9 (2)	24.0 ± 3.2	Emotion recognition task	Gray scale photographs of faces	Across sessions, stronger activation in left cerebellum in response to angry relative to neutral faces (1)	MNI
de Greck et al. (2012)	HC (Chinese and Germans)	16 (10) and 16 (10)	22.9 ± 1.2 and 23.3 ± 2.1*	Intentional empathy vs. skin color evaluation (baseline)	Colored photographs of faces	For both groups, stronger activation in bilateral cerebellum for angry faces relative to baseline (2)	TAL
Domes et al. (2010)	HC (oxytocin and placebo administration within participants)	16 (16)	24.2 ± 2.5	Emotional arousal rating	Photographs of faces	Across placebo and oxytocin administration, stronger activation in bilateral cerebellum in response to angry relative to neutral faces (2)	MNI

(*continued on next page*)

Table 1 (*continued*)

Study	Population	*N* (f)	Age (*M* ± *SD*)	Task	Stimuli	Included contrast (number of coordinates)	Reference space
Ewbank et al. (2009)	HC	24 (14)	26.1*	Same/different matching task with covert attention towards faces or houses	Gray scale photographs of faces and houses	Trait anxiety correlated with stronger activation in right cerebellum in response to attended angry faces relative to attended neutral faces (1)	MNI
Fehr, Achtziger, Roth, & Struber (2014)	HC	20 (0)	24.6 ± 4.4	Passive viewing	Videos of different valence	In final phase of video clip, stronger activation in right cerebellum in response to reactive-aggressive relative to neutral videos (2)	TAL
Grosbras & Paus (2006)	HC	20 (10)	28.6*	Passive viewing	Gray scale videos	Stronger activation in left cerebellum in response to angry faces relative to control condition (2)	TAL
Hadjikhani et al. (2017)	HC	20 (3)	23.5 ± 8.1	Passive viewing	Movies of facial expressions with or without fixation cross	Stronger activation of bilateral cerebellum when viewing angry faces with fixation cross relative to without fixation cross (10)	MNI
Kanat, Heinrichs, Schwarzwald, & Domes (2015)	HC (oxytocin and placebo administration within participants)	49 (0); 46 in final sample	23.6 ± 2.8	Emotion detection task	Gray scale photographs of faces with cue towards mouth or eyes	When cued towards eyes, stronger activation in left cerebellum in response to angry relative to neutral faces under placebo administration (1)	MNI
Koppe et al. (2015)	HC	30 (15)	24.2 ± 2.5	Gender and shape judgment task	Photographs of faces and images of shapes	Stronger activation in left cerebellum in response to angry faces relative to shapes (1)	MNI
Lin et al. (2016)	HC	16 (10)	22.6 ± 2.8	Gender judgment	Colored photographs of faces	Stronger activation in left cerebellum in response to angry relative to happy faces (1)	TAL
Luan Phan et al. (2013)	gSP and HC	21 (13) and 19 (9)	25.9 ± 5.5 and 27.0 ± 8.1	Emotional face matching task	Photographs of faces	Stronger activation in bilateral cerebellum in response to angry vs. happy faces for HCs compared to gSP (1)	MNI
McCloskey et al. (2016)	HC [IED]	20 (8) [20 (8)]	33.2* [32.8]*	Emotion identification	Gray scale photographs of faces	Stronger activation in bilateral cerebellum in response to angry faces relative to neutral faces (4)	MNI
Park, Lee, & Sohn (2017)	HC [alcohol abusers]	16 (0) [18 (0)]	50.1 ± 6.1 [49.8 ± 6.6]	Passive viewing	Videos of different valence	Stronger activation in right cerebellum in response to angry videos relative to neutral videos (1)	TAL
Pawliczek et al. (2013)	HC (high vs. low aggression)	39 (0)	22.2 ± 2.2 and 22.6 ± 2.2	Frustration task	Solvable vs. unsolvable anagrams	Stronger activation in bilateral cerebellum during unsolvable relative to solvable anagrams (3)	MNI
Radke et al. (2018)	MDD and HC	22 (9) and 22 (9)	34.5 ± 9.9 and 32.6 ± 10.9	Emotional state rating with varying personal relevance	Colored photographs of faces	During view-only condition, stronger activation in left cerebellum and weaker activation in right cerebellum in response to angry relative to neutral faces (2)	MNI
Tonnaer, Siep, Van Zutphen, Arntz, & Cima (2017)	VOF and HC	16 (0) and 18 (0)	35.8 ± 7.2 and 34.4 ± 13.4	Anger Articulated Thoughts During Simulated Situations paradigm in which participants either engaged in or regulated an elicited emotion	Audio files of emotional or neutral situations	Across both groups, stronger activation in left cerebellum in response to angry relative to neutral situations (1)	TAL
Wheaton, Fitzgerald, Phan, & Klumpp (2014)	gSAD and HC	23 (16) and 24 (13)	26.1 ± 6.7 and 25.0 ± 5.6	Letter identification task with emotional distractors	Six-letter strings and gray scale photographs	Across both groups, stronger activation in left cerebellum in response to angry relative to neutral distractors (1)	MNI

Note. Details provided in square brackets concern participants included in the respective study who, however, were not part of the contrast included in the analysis. gSAD = generalized social anxiety disorder. gSP = generalized social phobia. HC = healthy controls. IED = Intermittent Explosive Disorder. MDD = Major Depressive Disorder. MDMA = Methylenedioxymethamphetamine. MNI = Montreal Neurologic Institute reference space. TAL = Talairach reference space. VOF = violent offenders. *SD not reported.

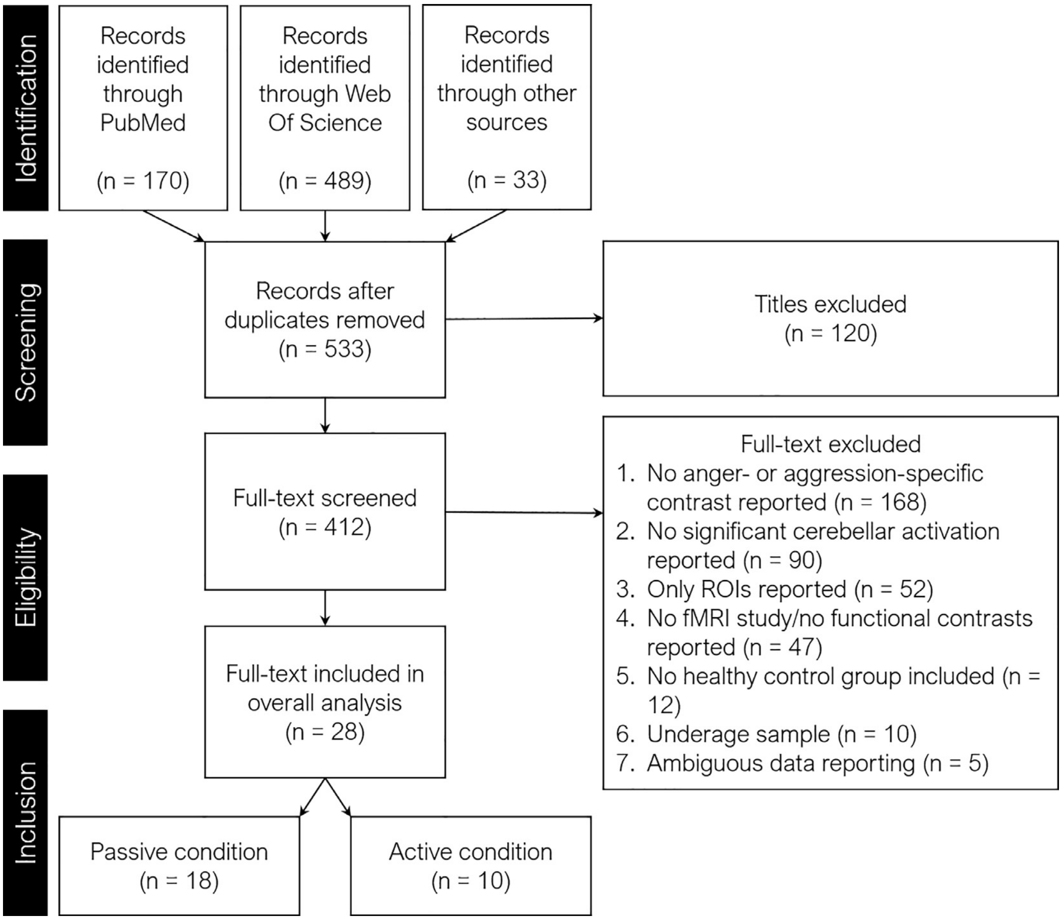

Fig. 1. PRISMA flowchart documenting the literature search.

Table 2
Results ALE analyses.

Condition	Threshold	#	Cluster size (mm^3)	*T*	Peak coordinates
Passive condition	.001	1	623	4.10	40, −64, −35
	.01	1	2181	4.14	38, −64, −34
		2	1493	3.28	−13, −78, −35
		3	1439	3.24	−29, −43, −51
Active condition	.001	1	986	6.27	17, −52, −19
		2	465	4.47	−30, −61, −27
		3	340	3.67	30, −50, −35
	.01	1	7391	36.0	24, −53, −28
		2	2116	3.53	−7, −53, −16

mapped to cerebellar flat maps using the SUIT toolbox (Diedrichsen and Zotow, 2015) in Matlab (Matlab R2019a).

3. Results

Table 2 reports the activation peaks of the significant clusters broken down by condition and cluster-forming threshold.

3.1. Passive condition: Anger and threat processing

Eighteen studies using anger and threat processing tasks reported 37 activation foci from 489 participants. The ALE analysis on this set using the conventional cluster forming threshold of $p < .001$ yielded one cluster in the right cerebellar hemisphere, specifically in Crus I and II. At a more lenient threshold ($p < .01$), a more widespread bilateral network in the posterior cerebellum emerged, encompassing paravermal and hemispheric regions of bilateral Crus I and II, right regions of lobule VI, and left regions of lobules VIIIA, VIIIB, and X. These regions show overlap with clusters associated with emotion processing from previous ALE meta-analyses (E et al., 2014; Guell et al., 2018), as well as clusters related to emotion and language processing, action observation, motor planning, and divided attention (King et al., 2019). Furthermore, the observed regions have been shown to be functionally connected to the frontoparietal, default mode, and somatomotor network (Buckner et al., 2011). Fig. 2 displays the significant clusters overlaid on a standard anatomical template of the cerebellum and Fig. 3 illustrates the findings mapped onto cerebellar flat maps.

3.2. Active condition: Aggression induction

The ten studies focusing on aggression induction reported 20 activation foci from 330 participants. The ALE analysis on this set using the conventional cluster forming threshold of $p < .001$ yielded three clusters in the bilateral anterior cerebellum, while the more lenient threshold of $p < .01$ additionally revealed a right-hemispheric cluster in Crus II and lobule VIIB. These regions overlap with emotion-related clusters observed in previous ALE meta-analyses (E et al., 2014; Stoodley and Schmahmann, 2009) as well as regions associated with motor planning, divided attention, active maintenance, and verbal fluency (King et al., 2019). Finally, locations containing significant clusters in the current analysis have been shown to be functionally connected to the somatomotor, frontoparietal, limbic, and ventral attention network in the cerebral cortex (Buckner et al., 2011).

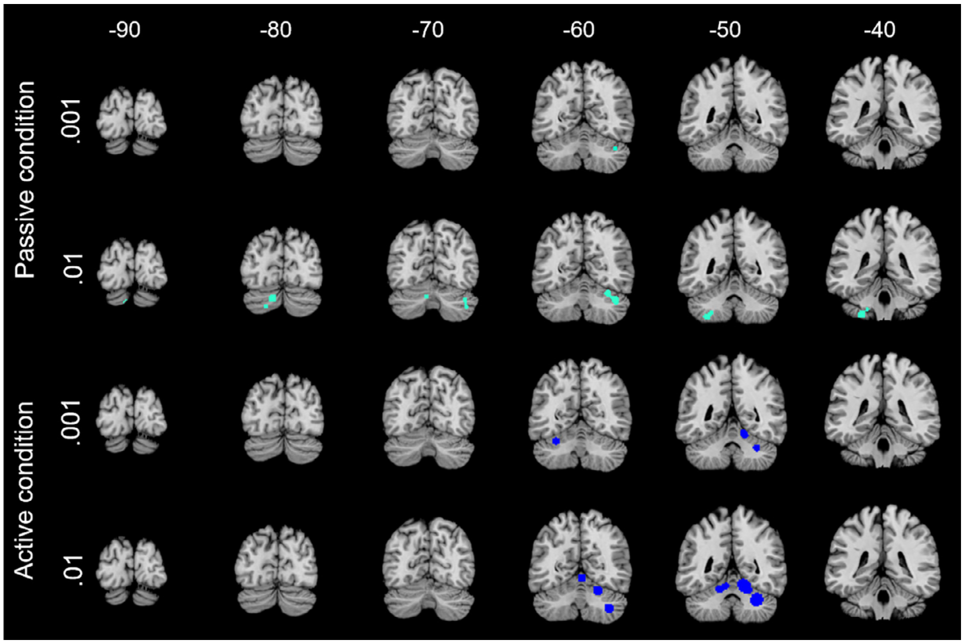

Fig. 2. ALE activation maps analysis on the passive condition (upper two panels) and active condition (lower two panels) for five different slices (y = −90, −80, −70, −60, −50, −40) and two different voxel thresholds, mapped onto coronal sections of the Colin27 brain. The left cerebellar hemisphere is shown on the left.

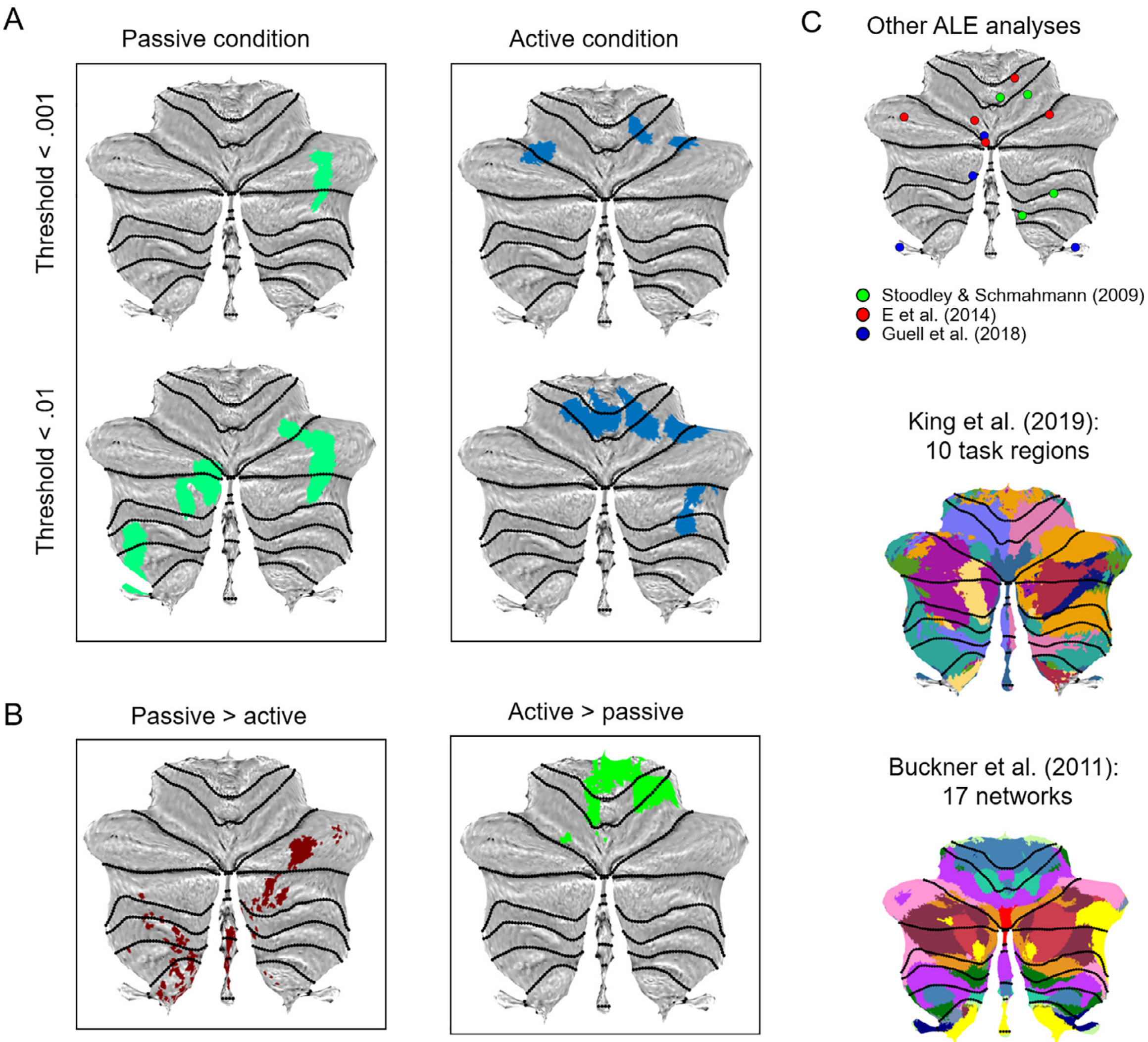

Fig. 3. ALE results projected on cerebellar flatmaps. (A) Significant clusters for the passive (left) and active condition (right). (B) Results from contrast analyses. (C) Results from previous functional and connectivity studies for comparison purposes.

3.3. Contrast analyses between active and passive conditions

To further evaluate condition-specific contributions, we performed subtraction analyses for the contrasts active versus passive and passive versus active (Fig. 3B). Results confirmed a large cluster in the anterior cerebellum specific to the active condition, as well as a more diffuse activation pattern extending from right Crus I to left lobule IX specific to the passive condition. Overall, these findings confirm the division of activation observed in the separate analyses reported above, namely that aggression-related behavior is primarily associated with activation of the anterior cerebellum, whereas more intrinsic processes associated with the experience and processing of anger and threat are confined to posterior cerebellar regions.

4. Discussion

The aim of the current study was to map cerebellar activation patterns associated with anger and aggression. Results showed dissociable patterns for overt aggressive behavior (i.e., the active condition) and the experience of anger and frustration (i.e., the passive condition), and indicate that activation in the active condition primarily clustered in the anterior cerebellum, whereas the passive condition demonstrated common activation peaks in the posterior cerebellum.

4.1. Anger in the cerebellum

Hemodynamic activity associated with the experience of angry and threatening contents was clustered in right Crus I and II. At a more liberal cluster threshold ($p < .01$) additional activation was observed in right lobule VI and left Crus I, II and lobules VIIIA, VIIIB, and X. These locations concur with emotion-related clusters reported by E et al. (2014) and Guell et al. (2018), but there was no overlap with the clusters obtained by Stoodley and Schmahmann (2009). This may be explained by the fact that the former two studies limited their analysis to negative emotional stimuli, while Stoodley and Schmahmann (2009) investigated a range of both positive and negative emotions. Further, our findings show overlap with task regions associated with emotion, language, and action observation (King et al., 2019), illustrating the cognitive aspects involved in anger and threat processing. In addition, the currently observed clusters have been shown to be functionally connected to the frontoparietal and the default mode network in the cerebral cortex (Buckner et al., 2011).

To further explore possible functional connections between the clusters observed in the current studies and other cortical regions and networks, we additionally used Neurosynth (https://neurosynth.org/locations/) to generate resting-state maps using the peak coordinates obtained in the ALE analysis thresholded at $p < .01$ as seeds (Fig. 4). This revealed additional associations with somatosensory and motor regions as well as the insula, angular gyrus, and brainstem (see upper panels of Fig. 4). While the brain stem regulates autonomic activity, the insular cortex has been implicated in the processing of subjective feelings and empathy (Uddin et al., 2017). Further, the angular gyrus is involved in the abstract representation of goal-directed social behavior (Spreng et al., 2009; Van Overwalle and Baetens, 2009).

Activation of the medial regions of the cerebellum, as displayed in the contrast analysis in Fig. 3B, may represent modulatory output signals to the limbic and insular circuit associated with homeostatic regulation, as well as appraisal processes during threat evaluation. These connections allow the cerebellum to integrate different information processing streams in parallel, potentially through functional connections to the temporoparietal junction (Van Overwalle et al., 2019, 2015). The involvement of the cerebellar lobules can be explained by emotional appraisal, as they contribute to assigning affective meaning to the emotional stimuli and prepare the body for action (Baumann and Mattingley, 2012; Stoodley and Schmahmann, 2010).

It is worth noting that the passive as compared to the active condition resulted in remarkably less cerebellar activation and connectivity patterns associated with motor behavior, but instead showed cerebellar links to cognitive, limbic, and social networks (see Figs. 3 and 4). Of particular interest is the significant activation observed in the left flocculonodular lobe (lobule X) of the cerebellum, which has been hypothesized to be sensitive to negative emotions (Guell et al., 2018; Schraa-Tam et al., 2012). Lobule X is considered part of the evolutionarily older cerebellum associated with primitive, threat-evaluating reactions like the fight-or-flight response (Schmahmann, 1991).

4.2. Aggression in the cerebellum

Aggressive responses as evoked through retaliating conditions could be localized to lobules V and VI of the rostral part of the cerebellum. The findings concur with previous ALE analyses examining emotion processing, which reported cluster peaks in similar regions (E et al., 2014; Stoodley and Schmahmann, 2009). Furthermore, an ALE meta-analysis on social cognition revealed a number of clusters in medial and lateral anterior regions as well as right Crus I/II associated with mirroring and mentalizing that are in close proximity of the regions found for the active condition in the current study (Van Overwalle et al., 2014; but see Van Overwalle et al., 2020, for a more medial localisation of mentalising and sequencing in right Crus II). Particularly the posterior clusters may reflect person- and situation-related abstraction processes which, in the current context, may be interpreted in terms of a cognitive evaluation of the use of an aggressive response. Alternatively, abstraction may also involve rumination and aggressive internal verbalization, thus reflecting a bottom-up outlet of perceived anger rather than top-down regulation thereof.

The obtained clusters in the present study can be mapped onto task regions associated with motor planning, divided attention, active maintenance, and verbal fluency (King et al., 2019), emphasizing the involvement of cognitive processes involved in aggressive behavior. This may, for instance, pertain to a targeted focus towards the source of aggression, verbalization of aggression-related thoughts, and evaluation of the arousal level. In terms of functional connectivity, they are localized in regions which have been shown to be connected to the somatomotor and, to a lesser extent, the frontoparietal network in the cerebral cortex (Buckner et al., 2011). A closer inspection of the functional connectivity patterns using the peak coordinates of the significant clusters as seeds (see lower panels of Fig. 4) confirmed functional connectivity to motor and prefrontal control networks, but additionally provided evidence for connections to the posterior cingulate, which is a prominent hub of the default mode network and has been linked to processing of emotional and noxious content (Vogt, 2005).

Furthermore, the current findings suggest that approach-related aggression is manifested in somatosensory regions of the cerebellum, which has been demonstrated to be functionally connected to somatosensory cortical regions during elicited aggression (Wong et al., 2019). Since lobule VI is implicated in working memory processes and active maintenance of information, the right-sided activation of lobules V and VI may represent sensorimotor processes related to approach motivation caused by frustration and/or provocation that increases the likelihood of a coordinated strike. This highlights the transition from motivational tendencies to motor execution (Balsters and Ramnani, 2008; Belkhiria et al., 2017). On a speculative account, lateral regions of lobule VI may perhaps even be one of the critical nodes governing the transition from non-motor (passive) to motor (active) processes that leads to a coordinated strike. Precision functional mapping of resting-state signals in the brain has shown that there is a relatively short time lag of ~130 ms between signals emerging in motor and somatosensory networks of the cerebral cortex and connected regions in the cerebellum (Marek et al., 2018). This accelerated signal transfer – as compared to a mean lag of 300–400 ms between default mode, frontoparietal, and attention networks and their cerebellar counterparts (Marek et al., 2018)

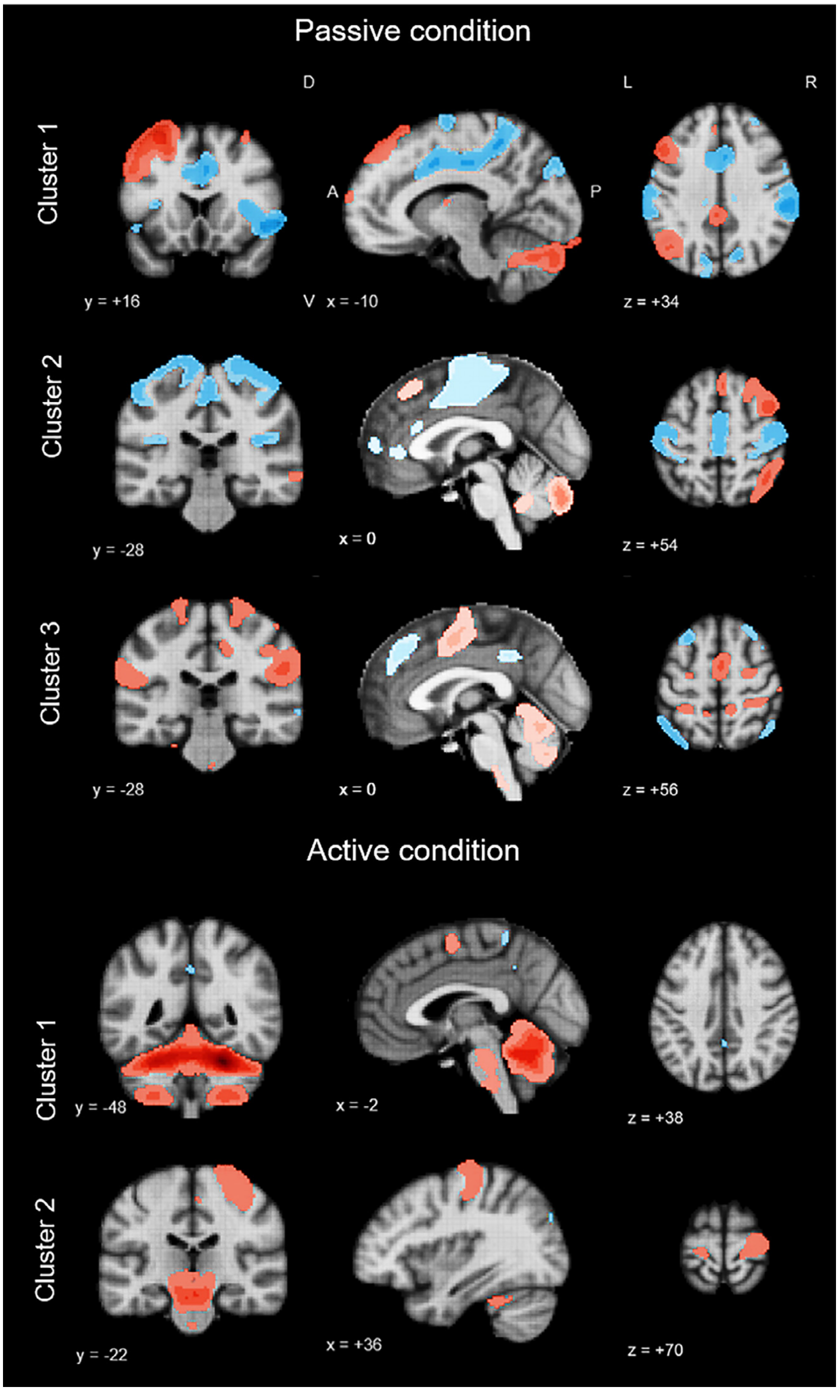

Fig. 4. Resting-state maps based on peak coordinates for the significant clusters obtained for the ALE analysis for the passive condition (top) and active condition (bottom; cluster-forming threshold p < .01). Blue shades indicate negative Pearson correlation coefficients between the respective seed and the associated brain region; red shades indicate positive correlations. Displayed regions indicate absolute correlations higher than 0.1.

– supports the idea that aggressive behavior is a rapidly unfolding process which occurs prior to the onset of domain-general, higher-order control mechanisms aimed at adaptively supervising cortical processes. While the present analysis does not warrant any temporal inferences, we can speculate that aggressive behavior as measured within the current context may reflect an impulsive reaction strongly grounded in evolutionarily primitive behavior associated with motor and limbic processing, whereas the application of cognitive control helps to regulate an escalation of the executed behavior. The observed cerebellar activity patterns may represent efferent copies of non-motor (symbolic) and motor commands originating from the mid- and forebrain regions, allowing the cerebellum to coordinate and monitor the striatal and cortico-limbic routines involved in the experience and expression of anger. Additionally, part of this motor-related activity may involve the difference in neural activation related to motor responses associated with retaliation as compared to the higher number of motor responses associated with other aspects of task performance.

4.3. *Limitations*

Several limitations of the current study should be discussed. First, the heterogeneous nature of the tasks and studies makes it difficult to make a clear distinction between affective defensive and predatory forms of aggression. Based on the studies that were used in the current meta-analysis, the observed pattern of aggression-related activity may be associated with predatory (proactive) aggression. In line with clinical studies, we hypothesized that affective defensive (reactive) aggression primarily involves the medial parts of lobule IV (Heath et al., 1978; Schmahmann and Sherman, 1998).

Second, the analyses reported here are based on a small number of studies. Although the findings provide interesting grounds for speculation and leads for further research, the statistical power is likely too small to draw any firm conclusions (Eickhoff et al., 2016; Müller et al., 2018) and results should therefore be treated cautiously.

Third, the current results do not exclude the possibility that emotions other than anger map onto similar cerebellar regions. Note, however, that the contrast analyses fed into the analyses for the passive condition involved comparisons of angry against both happy or neutral facial expressions (see Table 1), so we deem it unlikely that at least non-negative emotions would map onto the same clusters reported here. Furthermore, Baumann and Mattingley (2012) reported both overlapping and distinct cerebellar clusters for five different emotions, suggesting that emotional representations dissociate in the cerebellum. This is in line with a recent account of multiple functionality within the cerebellum (Diedrichsen et al., 2019), which assumes that despite a highly uniform structural constitution, the cerebellum is responsible for a plethora of different functions which cannot be subsumed under one general computation. Alternatively, however, such a division of labor may in fact be explained within the framework of a generic process, which executes comparable actions across a variety of domains (Schmahmann, 1996). The traditionally assumed role of the cerebellum in understanding sequences and making predictions (Leggio and Molinari, 2015) has, for instance, been successfully adapted to the domain of social cognition, in which it is now assumed that inferring one's and other's mental states equally relies on sequencing human actions to correctly interpret social situations and adapt to novel circumstances appropriately (Heleven et al., 2019; Pu et al., 2020; Van Overwalle et al., 2019; Van Overwalle et al., 2020). Likewise, emotional processes may rely on such an overarching concept, in the sense that it requires the sequential interpretation and processing of the available information in order to steer appropriate outcomes. Importantly, neither multiple nor single functionality of the cerebellum necessitate strictly uniform representations of different stimuli within the cerebellum.

Fourth, the current analyses draw from studies including both healthy and clinical populations (see Table 1). Although we took care to only include contrasts in which patient populations and respective control groups did not differ in terms of cerebellar activation (i.e., the analysis included only main effects of the experimental condition), we cannot exclude the possibility that intrinsic functional and structural differences between the groups may have contributed to the results. With the few studies that exist on this topic, it is presently not possible to dissociate potential differences between healthy and clinical individuals.

4.4. Conclusion

This study is the first to synthesize functional neuroimaging studies on anger and aggression in the cerebellum, confirming the role of distinct anatomical regions in this domain. Future research should ensure that the cerebellum is properly included in scanning protocols and analysis pipelines (Schlerf et al., 2014) as not to miss potentially valuable information about this versatile structure in studying the neuroanatomic correlates of human anger and aggression.

Declaration of Competing Interest

None.

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Data availability statement

Data pertaining to this manuscript are available at https://osf.io/pc3ft/

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