Journal of Psychiatric Research 159 (2023) 42–49

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Lower cerebello-cortical functional connectivity in veterans with reactive aggression symptoms: A pilot study

E.M.L. Wolfs [a,*], R. van Lutterveld [b,c], T. Varkevisser [b,c,d], J. Klaus [a], E. Geuze [b,c], D.J.L.G. Schutter [a]

[a] Department of Experimental Psychology, Helmholtz Institute, Utrecht University, Heidelberglaan 1, 3584 CS, Utrecht, the Netherlands
[b] Department of Psychiatry, UMC Utrecht Brain Center, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, the Netherlands
[c] Brain Research & Innovation Centre, Ministry of Defence, Lundlaan 1, 3584 EZ, Utrecht, the Netherlands
[d] Research and Documentation Centre, Ministry of Justice and Security, Koningskade 4, 2596 AA, The Hague, the Netherlands

ARTICLE INFO

Keywords:
Aggression
Cerebellum
Deep cerebellar nuclei
Orbitofrontal cortex
Resting state fMRI
Veterans

ABSTRACT

A significant number of veterans experience irritability and aggression symptoms as a result of being exposed to extremely stressful and life-threatening situations. In addition to the well-established involvement of the brain's cortico-subcortical circuit in aggression-related behaviours, a role of the deep cerebellar nuclei (DCN) in reactive aggression has been suggested. In the present study, seed-based resting-state functional connectivity between the DCN and cortico-subcortical areas was explored in veterans with and without reactive aggression symptoms. Nineteen male veterans with reactive aggression symptoms and twenty-two control veterans without reactive aggression symptoms underwent 3T resting-state functional MRI scans. Region-of-interest (ROI) analyses that included the amygdala, hypothalamus and periaqueductal grey as ROIs did not yield significant group-related differences in resting-state functional connectivity with the DCN. However, exploratory whole-brain analysis showed that veterans with reactive aggression symptoms exhibited lower functional connectivity between the DCN and the orbitofrontal cortex compared to control veterans. Our findings provide preliminary evidence for the possible involvement of a cerebello-prefrontal pathway in reactive aggression in male veterans.

1. Introduction

A significant proportion of veterans exhibit high levels of irritability and reactive aggression symptoms following their deployment (MacManus et al., 2015; Orth and Wieland, 2006; Reijnen et al., 2015). Reduced impulse control and increased anger in veterans have been suggested to result at least in part from trauma-related experiences (Miles et al., 2017; Siever, 2008). Neuroscientific research points towards the involvement of several cortical and subcortical regions in impulse control and expressions of aggressive behaviour during situations of threat, frustration and provocation including, most notably, the prefrontal cortex (PFC), hypothalamus, amygdala and periaqueductal grey (PAG) (Davidson et al., 2000; Lischinsky and Lin, 2020). The amygdala, hypothalamus and PAG work together to detect threats (Öhman, 2005), integrate sensory and spatial information and to guide social behaviour (Krzywkowski et al., 2020) through (defensive) responses (Esteban Masferrer et al., 2020; Panksepp and Biven, 2012). Specifically, responsivity to threat (e.g., freeze vs. escape) has been shown to be regulated by the basolateral nucleus of the amygdala via the central amygdala (Terburg et al., 2018). In addition, the basolateral and centromedial nuclei of the human amygdala are associated with sensory input processing and response preparation. The superficial nuclei which are located adjacent to the basolateral nuclei of the amygdala have been linked to the processing of olfactory, social and reward cues (Bzdok et al., 2013). Interestingly, evidence has been provided that veterans with reactive aggression symptoms exhibit lower functional PFC-amygdala connectivity as compared to veterans without symptoms of reactive aggression (Varkevisser et al., 2017). Heightened subcortical stress reactivity to threat, in conjunction with reduced cortical regulatory mechanisms, has been suggested as one of the possible mechanisms underlying aggressive behaviour (Lischinsky and Lin, 2020; Siever, 2008).

In addition to the (sub)cortical structures, the often-overlooked cerebellum is increasingly linked to aggression (Kruithof et al., 2022). The first empirical observations date back to the second half of the previous century when researchers showed that electric stimulation of

* Corresponding author.
E-mail address: e.m.l.wolfs@uu.nl (E.M.L. Wolfs).

https://doi.org/10.1016/j.jpsychires.2023.01.023
Received 26 July 2022; Received in revised form 5 December 2022; Accepted 10 January 2023
Available online 11 January 2023

the deep cerebellar nuclei (DCN) in cats induced sham rage, predatory attacks and autonomic responses (Reis et al., 1973; Zanchetti and Zoccolini, 1954). The DCN are a collection of nuclei that are responsible for the main cerebellar output (Habas et al., 2016). In addition to the reciprocal connections between the DCN and the inferior olive, the DCN relay the input signals from the cerebellar cortex to limbic and thalamo-cortical regions that form closed loops through the pontine nuclei (Allen and Tsukahara, 1974). In line with previous observations in psychiatric patients displaying fewer aggressive acts during subdural electric stimulation of the medial cerebellar cortex (Heath, 1977; Heath et al., 1980), DCN activity is thought to be inhibited by the medial cerebellum or 'vermis' (Jackman et al., 2020). More recently, an optogenetic study in mice demonstrated that inactivation of the cerebellar vermis increased aggressive behaviour during threat, while lower threat-related aggression was seen when neural activity of this region was artificially increased (Jackman et al., 2020). Furthermore, these intracranial stimulation studies concur with findings of neuropsychological studies in humans which show that cerebellar damage can cause blunting of affect, reductions in impulse control, executive dysfunctions and notable increases of aggressive behaviour (Levisohn et al., 2000; Schmahmann and Sherman, 1998; Tessier et al., 2015; Tonna et al., 2014). In non-human primates, however, lesions in the cerebellar vermis can have a taming effect on aggressive behaviour (Berman et al., 1974). Recent structural and task-based functional magnetic resonance imaging (fMRI) findings in humans have complemented the proposed relation between the cerebellum and aggression (Klaus and Schutter, 2021; Wolfs et al., 2022).

To further examine the intrinsic functional connections of the cerebellum, resting-state fMRI can be used (van den Heuvel and Hulshoff Pol, 2010). While the use of resting-state fMRI to study cerebellar functional connectivity in aggression is still scarce, there is some evidence that suggests that abnormal (sub)cortico-cerebellar connectivity patterns are associated with impulse control and aggression (Leutgeb et al., 2016). In a more recent study, functional connectivity with the supplementary motor area (SMA), hippocampus and orbitofrontal cortex (OFC) as seed regions was examined in patients with Tourette disorder (TD) suffering from rage attacks (Atkinson-Clement et al., 2020). Rage attacks are characterised by sudden outbursts of verbal or physical aggression and are a common condition in patients with motor- and vocal-related tics (Conte et al., 2020). The functional connectivity analyses showed that TD patients with rage attacks as compared to TD patients without rage attacks displayed reduced connectivity between the OFC and lateral cerebellum and between the hippocampus and cerebellar vermis (Atkinson-Clement et al., 2020). Aberrant cerebellar resting-state connectivity is suggested to be part of a dysfunctional neural network involved in arousal, context updating, impulse control and behavioural flexibility (Atkinson-Clement et al., 2020; Klaus and Schutter, 2021). In the cerebellar cortex, the posterior cerebellum is associated with the functional networks underlying these affective and cognitive functions, such as the salience network and default mode network (Buckner et al., 2011; Habas, 2021; Habas et al., 2009; Marek and Greene, 2021), whereas the anterior cerebellum is generally linked to the sensorimotor network (Schmahmann, 2019). The DCN, being the main target inputs of the cerebellar cortex as well as the main output regions of the cerebellum to extracerebellar regions, are functionally connected to the salience, default mode and sensorimotor networks (Guell et al., 2019; Habas et al., 2009). More specifically, an increased tendency to approach goals and rewards was associated with decreased connectivity between the cerebellum and cortical regions of the salience network (i.e., dorsolateral prefrontal cortex, superior frontal cortex, fronto-polar cortex, and intraparietal cortex) (Abdallah et al., 2020). Decreased cerebellar connectivity has also been shown for regions that are part of the executive control, social cognition and emotion processing networks (i.e., parahippocampal gyrus, precuneus, cingulate gyrus and superior temporal gyrus) in obsessive compulsive disorder (Xu et al., 2019). Additionally, functional connections have been reported between the cerebellum and arousal nuclei in the brainstem in healthy adults (Singh et al., 2022).

In the present study, we set out to explore altered cerebello-subcortico-cortical functional connectivity in veterans who struggle with reactive aggression. We hypothesized that veterans with reactive aggression symptoms show decreased resting-state functional connectivity between the DCN and the amygdala, hypothalamus and PAG compared to veterans without aggression symptoms. Furthermore, we performed a whole-brain cortical connectivity analysis to explore potential reductions in functional DCN-cortical coupling (Atkinson-Clement et al., 2020) in veterans with reactive aggression symptoms compared to veterans without reactive aggression symptoms.

2. Methods

2.1. Participants

Twenty-eight male veterans with reactive aggression symptoms and thirty age-matched male veterans without aggression symptoms were recruited from four out-patient clinics of the Military Mental Healthcare Organization in Utrecht, the Netherlands. The present study sample was taken from a previous research project on reactive aggression in veterans focused on fronto-limbic regions (Varkevisser et al., 2017). As the cerebellum was not the main focus of this initial research project, the posterior fossa was not always completely scanned and eight veterans with aggressive symptoms and eight control veterans were excluded as the DCN were not within the participant's MRI scan field of view. One additional veteran with aggressive symptoms was excluded because we could not ascertain wakefulness for the entire resting-state scan. Reactive aggression was classified using the criteria for intermittent explosive disorder (see Coccaro, 2011, 2012): (1) verbal or physical aggression towards other people occurring at least twice weekly on average for one month; or three episodes of physical assault over a one year period; (2) the degree of aggressiveness is grossly out of proportion; (3) the aggressive behaviour is impulsive (not premeditated); (4) the aggressive behaviour causes either distress in the individual or impairment in occupational or interpersonal functioning. In the control group, there were no anger- and aggression-related pathologies or current DSM-IV Axis-I diagnoses. To be included in this study, individuals in both groups had to be MRI scanner compatible, between 18 and 50 years, and have been on military deployment for at least four months. The study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht and was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

2.2. Behavioural assessment and analyses

For all veterans, the demographic characteristics age, number of deployments, duration of deployment and time since last deployment were recorded. Aggressive behaviour and personality were measured with the Dutch translations of the Buss-Perry Aggression questionnaire (BPA; Buss and Perry, 1992; Dutch version: Meesters et al., 1996) and the State-Trait Anger Expression Inventory (STAXI-2; Spielberger et al., 1999; Dutch version: Hovens et al., 2014). The BPA is a self-report questionnaire (29 items) that measures physical aggression (9 items), verbal aggression (5 items), anger (7 items) and hostility (8 items). Participants respond on a five-point scale ranging from "extremely uncharacteristic of me" (1) to "extremely characteristic of me" (5). Higher BPA scores correspond to higher levels of aggression. The STAXI-2 is a self-report questionnaire (57 items) that assesses a person's angry feelings at the time (state anger) (15 items) and a person's predisposition to become angry (trait anger) (10 items). Participants respond on a four-point scale ranging from "almost never" (1) to "almost always" (4). Higher STAXI-2 scores correspond to more intense feelings of anger, both verbally and physically. The Mood and Anxiety Symptom

Questionnaire (MASQ; Watson and Clark, 1991; Dutch version: de Beurs et al., 2007) was used to quantify anxiety and depressive symptoms on a five-point scale ranging from "not at all" (1) to "extremely" (5). Higher scores on the MASQ corresponded to stronger symptoms of anxious arousal and anhedonic depression.

To evaluate group differences in demographic characteristics (age, number of deployments, duration of deployment and time since last deployment), aggression scores (BPA and STAXI-2) and depressive/anxious symptoms (MASQ), two-sample *t* tests were used for parametric data, Mann-Whitney *U* tests were used for non-parametric data and Fisher's exact tests were used for categorical data. These analyses were performed using R version 3.6.0 in RStudio version 1.2.1335 for Windows (RStudio Team, 2018). The alpha level of statistical significance was set at 0.05 (two-tailed).

2.3. Image acquisition

All images were acquired on a 3T Philips Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands). Structural T1-weighted images were acquired with a 3D sensitivity encoding sequence (SENSE, TR = 10 ms, TE = 4.6 ms, flip angle = 8°, voxel size = 0.8 × 0.8 × 0.8 mm, slices sagittal orientation = 200, FOV = 240 × 240 × 160, matrix = 304 × 299). Functional resting-state images were acquired with T2* echo planar imaging sequence (EPI, TR = 1600 ms, TE = 23 ms, flip angle = 72.5°, voxel size = 4.0 × 4.0 × 4.0 mm, 30 transverse slices interleaved, FOV = 256 × 208 × 120, matrix = 64 × 64, scanning time = 8.53 min). During the resting-state scan, participants were instructed to focus on a fixation cross displayed on the computer screen and let their minds wander.

2.4. Image preprocessing

All images were preprocessed and analysed using FSL (FMRIB's Software Library, Oxford, UK) version 6.0.3 (Jenkinson et al., 2012). Non-brain structures were removed from the images with the Brain Extraction Tool (BET2) (Smith, 2002). The fMRI Expert Analysis Tool (FEAT) (Woolrich et al., 2001) was used to realign and smoothen the functional images with an isotropic gaussian filter kernel with 2 mm full width at half maximum (FWHM). The mean signal of each voxel was normalised by grand mean scaling. Next, images were registered to the subject's structural image and to standard MNI152 image space using FMRIB's Linear Image Registration Tool (FLIRT) (Jenkinson et al., 2002; Jenkinson and Smith, 2001). Registration from structural images to standard space was further optimized by nonlinear registration (FNIRT) (Andersson et al., 2007). ICA-AROMA (Pruim et al., 2015) was used to remove motion-related noise from the functional images. ICA-AROMA provided automatic labelling as noise or signal for the generated independent components based on frequency spectra (e.g., distribution of frequency power), time-courses (e.g., regularity of oscillatory patterns) and spatial maps (e.g., locations and dimensions of clusters) (Griffanti et al., 2017; Pruim et al., 2015). Manual reclassification of these independent components was performed to check if the components were correctly labeled as noise or signal (Griffanti et al., 2017). Variance assigned to noise was removed in the data by non-aggressive ICA-AROMA denoising. Additionally, nuisance regression was used to correct for white matter and cerebrospinal fluid (CSF) signals. Lastly, denoised data was high-pass filtered at 0.01 Hz and additionally smoothed with a relatively small kernel (final FWHM = 4 mm) to avoid too much signal smearing in our relatively small regions of interest.

2.5. Regions-of-interest

Our DCN seed region of interest was manually segmented for each participant at the medial cerebellum, above lobule X and the 4th ventricle, close to the cerebellar outflow pathways, using the MRI atlas of the Human Cerebellum (Schmahmann et al., 2000) (see Supplementary Fig. 1). Our functional data did not include resting-state activity of the lateral cerebellar hemispheres, therefore further analyses on cerebellar lobules could not be taken into account.

To evaluate functional connectivity between the cerebellum and the main subcortical regions of the aggression circuit, the hypothalamus, amygdala and PAG were chosen as regions-of-interest (ROIs). In line with the previous study on the larger sample of veterans (Varkevisser et al., 2017), the subsections of the amygdala (basolateral, centromedial and superficial) were defined by SPM12's Anatomy Toolbox (Amunts et al., 2005; Eickhoff et al., 2005) for the left and right hemisphere separately. The hypothalamus was set as a sphere with 12 mm radius in the middle of both hemispheres located at MNI coordinates $x = 0$, $y = -4$, $z = -10$ to include the different hypothalamic nuclei (Baroncini et al., 2012; Kullmann et al., 2014). The PAG was set as a sphere with 3.72 mm radius located at MNI coordinates $x = 1$, $y = -29$, $z = -12$, in line with Varkevisser et al. (2017) and a meta-analysis by Linnman et al. (2012).

2.6. Subject-level: Seed-based correlation

Average time-series were extracted from each participant's DCN seed and ROIs. These time-series were used as regressors in the General Linear Models (GLM) along with their temporal derivatives. Two subject-level analyses were performed: Region-Of-Interest (ROI) and exploratory whole-brain. Temporal autocorrelation in the GLM was removed with FMRIB's Improved Linear Model (FILM) (Woolrich et al., 2001). For the ROI analyses, separate GLMs were analysed with the segmented amygdala regions, hypothalamus and PAG to mask the *Z*-stat images before thresholding. For the exploratory whole-brain analysis, an MNI grey matter mask was used before thresholding to confine the search space to grey matter structures exclusively.

2.7. Group comparison: ROI and whole-brain analyses

Statistical contrast maps that were registered to standard MNI152 space were used for group analyses. Differences in functional connectivity of the DCN with the hypothalamus, PAG and amygdala were examined between the veterans with and veterans without reactive aggression. In addition to the ROIs, an exploratory whole-brain analysis was performed to evaluate group differences in functional connectivity between the DCN and other (sub)cortical regions. For both analyses, mixed effects modelling at the group level was performed with FMRIB's Local Analysis of Mixed effects (FLAME) 1 + 2 in FEAT with automatic outlier de-weighting (Woolrich et al., 2004). All statistical maps were Gaussianised to the normal *Z*-distribution (Worsley, 2001). For the group level contrast images, a cluster-forming threshold of $Z > 2.3$ ($p < 0.01$) and a family-wise error (FWE) corrected cluster significance threshold of $p < 0.05$ (additionally FDR-corrected for multiple ROIs; Benjamini and Hochberg, 1995) were employed (Worsley, 2001). For whole-brain analyses, a cluster-forming threshold of $Z > 2.3$ and a corrected cluster significance threshold of $p < 0.05$ was considered significant (Worsley, 2001).

Additionally, functional connectivity measures were linked to behavioural questionnaire outcomes. Pearson's correlations between DCN-subcortical functional connectivity measures and behavioural scores on the BPA/STAXI-2 questionnaires were performed. Functional connectivity measures were considered outliers if they deviated by more than 3 standard deviations from the mean. The statistical significance with FDR correction for these exploratory analyses was set at $p < 0.05$ (two-tailed; Benjamini and Hochberg, 1995).

2.8. Additional analyses

While we corrected for motion-related artefacts, residual motion can still lead to noise in the data (Byrge and Kennedy, 2018). For each participant, fractional displacement (FD) values were calculated by

averaging the rotation/translation parameter differences with matrix RMS formulation (Jenkinson et al., 2002) in FSL. A Mann-Whitney *U* test was performed to examine a group difference in median FD values. Additionally, the percentage of total timepoints with FD measures exceeding the 0.2 mm threshold, which is a commonly used threshold to define motion outliers (e.g., Chen et al., 2018; Ciric et al., 2018; van Lutterveld et al., 2022), were compared between groups. To further test whether the results from our study were confounded by motion artefacts, median FD values of each participant were correlated with their average functional connectivity outcomes and measures of aggressive behaviour.

For the functional connectivity analysis, a potential confound of medication use was examined by visual inspection of the data distribution and performing an outlier check ($M \pm 3$ *SD*).

Table 1
Demographic and psychometric characteristics of the study population.

	Reactive aggressive veterans (n = 19)	Control veterans (n = 22)	Difference
Demographic data			
Age	35.0 [29.5; 37.0]	29.5 [26.3; 39.8]	$p = 0.555$[a]
Number of deployments (n)	2.0 [1.0; 3.0]	2.0 [1.0; 2.8]	$p = 0.989$[a]
Duration of deployment (months)	8.0 [5.0; 11.5]†	9.0 [5.0; 11.3]‡	$p = 0.712$[a]
Time since last deployment (years)	6.0 [5.5; 8.5]	6.0 [5.3; 7.0]	$p = 0.424$[a]
Medication use	4 (21%)	0 (0%)	**$p = 0.014$**[b]
Anti-depressant/SSRI	4 (21%)	0 (0%)	
Anti-anxiety/ Benzodiazepines	2 (11%)	0 (0%)	
Methylphenidate	1 (5%)	0 (0%)	
Psychometric data			
BPA total	93.0 [84.0; 106.5]	53.0 [48.0; 56.0]	**$p < 0.001$**[c]
BPA physical aggression	29.0 [26.0; 37.0]	17.5 [16.0; 20.5]	**$p < 0.001$**[c]
BPA verbal aggression	14.0 [13.0; 18.0]	11.0 [11.0; 12.0]	**$p < 0.001$**[c]
BPA anger	25.0 [23.0; 27.5]	11.0 [10.0; 12.0]	**$p < 0.001$**[a]
BPA hostility	23.0 [18.5; 28.0]	11.0 [10.0; 14.0]	**$p < 0.001$**[a]
STAXI-2 total	116.0 [111.5; 134.0]	109.0 [100.8; 111.0]	**$p < 0.001$**[a]
STAXI-2 state	18.0 [15.0; 27.5]	15.0 [15.0; 15.0]	**$p < 0.001$**[a]
STAXI-2 trait	23.0 [19.0; 28.5]	11.5 [10.0; 13.0]	**$p < 0.001$**[a]
MASQ anxious arousal	24.0 [20.0; 33.0]	17.0 [17.0; 19.0]	**$p < 0.001$**[a]
MASQ anhedonic depression	72.0 [64.5; 78.0]	39.5 [37.0; 44.0]	**$p < 0.001$**[c]

Data are presented as median [interquartile range] for continuous and as number (percentage of total) for categorical variables. Abbreviations: BPA = Buss-Perry Aggression questionnaire; MASQ = Mood and Anxiety Symptom Questionnaire; SSRI = Selective Serotonin Reuptake Inhibitor; STAXI = State-Trait Anger Expression Inventory.
† data available in 17 individuals; ‡ data available in 21 individuals.
[a] Mann-Whitney *U* test.
[b] Fisher's exact test.
[c] two-sample *t*-test.

3. Results

3.1. Study population

Demographics of the study population are shown in Table 1. The groups did not differ in age, sex, number of deployments, time since last deployment or duration of deployments. Veterans with reactive aggression symptoms showed significantly higher BPA aggression, STAXI-2 state and trait anger and MASQ anxiety and depression scores compared to control veterans ($ps < 0.001$, Table 1).

3.2. Brain-behaviour associations

No significant group differences in functional connectivity of the DCN with either the hypothalamus, PAG or the basolateral, centromedial and superior nuclei of the amygdala were observed between veterans with and without reactive aggression symptoms ($ps > 0.05$). Across the whole sample, for the correlations between ROI functional connectivity measures and the questionnaires, two participants were considered outliers. In the remaining thirty-nine participants, cerebellar-subcortical functional connectivity did not significantly correlate with scores on the BPA or STAXI-2 ($ps > 0.05$).

The exploratory whole-brain analysis showed that functional connectivity between the DCN and a prefrontal cluster was significantly decreased in veterans with aggression symptoms compared to controls (Fig. 1). The Z_{max} ($Z = 3.3$) location of the cluster ($x = -10$, $y = 42$, $z = -16$; 338 voxels, $p = 0.041$) corresponded to the left orbitofrontal cortex ($P(\text{OFC}|Z_{max}) = 0.86$) in the Neurosynth meta-analysis maps (Yarkoni et al., 2011). This cluster did not survive the more conservative cluster-forming threshold of $Z > 3.1$. DCN-OFC functional connectivity measures were negatively correlated to BPA and MASQ scores (see Supplementary results). Notably, depressive and anxious symptoms as measured with the MASQ did not mediate the DCN-OFC functional connectivity group difference (see Supplementary results).

3.3. Additional analyses

There was no significant group difference in median FD values between veterans with (median FD [interquartile range (IQR)] = 0.08 [0.06; 0.10]) and without (median FD [IQR] = 0.07 [0.06; 0.09]) aggressive symptoms ($Z = 0.71$, $p = 0.480$). The percentage of high FD values (>0.2 mm, aggressive veterans: median [interquartile range, IQR]: 1.9 [0.8; 9.2]; control veterans: 3.6 [1.3; 5.4]) did not differ between groups ($Z = -0.52$, $p = 0.600$). Furthermore, there was no correlation between median FD values and functional connectivity measures between the DCN and OFC ($r = 0.05$, $p = 0.748$) or aggression measures (BPA total score: $r = -0.06$, $p = 0.705$; STAXI total score: $r = -0.05$, $p = 0.750$). These results showed that our findings are unlikely to be explained by (residual) effects of motion-related noise.

In our sample, four veterans were present users of psycho-active medication (Table 1) (all four used anti-depressant medication, additionally one used methylphenidate and two used anti-anxiety medication). Visual inspection of the data distribution in aggressive veterans group showed no indication of clustering (see Fig. 1). Also, the functional connectivity values for these cases fell within 2 standard deviations from the mean. These observations indicated that the observed cerebello-OFC group difference was not driven by medication use.

4. Discussion

In the present study cerebello-subcortico-cortical resting-state functional connectivity was compared between veterans with- and without reactive aggression symptoms. No evidence was found for altered cerebello-subcortical functional connectivity in veterans with reactive aggression symptoms. Exploratory whole-brain analyses, however, demonstrated decreased connectivity between the DCN and OFC in

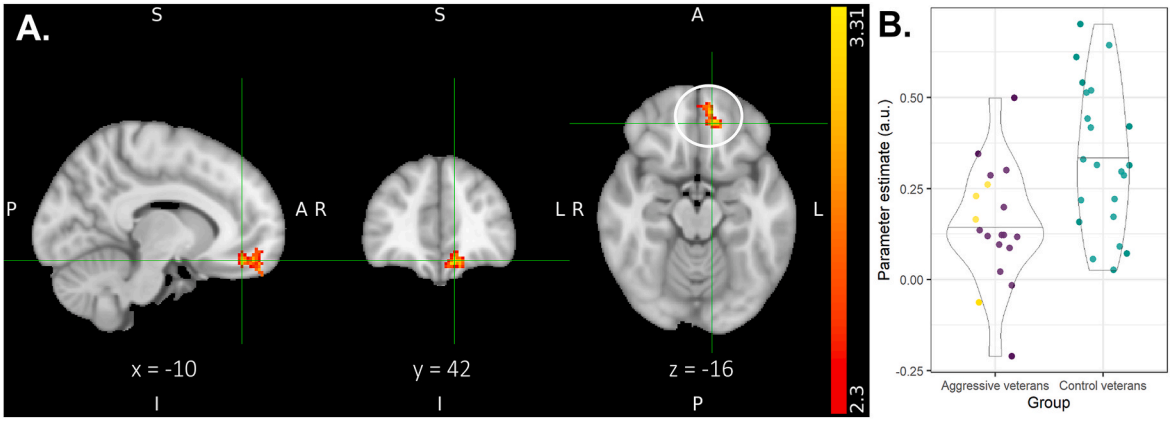

Fig. 1. (A) Reduction in DCN-prefrontal functional connectivity at $x = -10$, $y = 42$, $z = -16$ in veterans with reactive aggression symptoms compared to control veterans. (B) Mean parameter estimates of the cluster, broken down by veteran group. Purple dots represent the veterans with reactive aggression symptoms, yellow dots represent the veterans with reactive aggression symptoms currently on psycho-active medication and green dots represent the control veterans. A.u.: arbitrary units.

veterans with reactive aggression symptoms as compared to control veterans.

We did not observe group differences in functional connectivity measures between the DCN and amygdala, hypothalamus or PAG, nor did functional connectivity measures correlate with self-reported levels of anger and aggression. In contrast with our results, previous research has found evidence for increased functional connectivity between the cerebellum and amygdala in violent offenders compared to non-violent controls (Leutgeb et al., 2016). In addition, in healthy volunteers, increased functional connectivity between the cerebellum and amygdala has been related to increased behavioural inhibition (Roy et al., 2014). A more direct functional relationship between the DCN and hypothalamus has been demonstrated in animals, where electrical stimulation of the DCN was found to increase activity in the hypothalamus (Zanchetti and Zoccolini, 1954). In the present study, a DCN seed was used contrary to the cerebellar cortex seed in previous studies (Leutgeb et al., 2016; Roy et al., 2014). Furthermore, our sample exclusively included well-trained military veterans, who constitute a different population than the violent offenders investigated by Leutgeb et al. (2016). Additionally, it is conceivable that veterans with aggression symptoms did not show differences in DCN-subcortical functional connectivity in the absence of provocation, when no increased arousal, autonomic responses or aggressive behaviour occur. Available literature in cortico-limbic regions suggests that functional connectivity changes when arousal levels were reported higher (Paret et al., 2016) or after laboratory exposure to violence (Dark et al., 2020). Moreover, the absence of altered connectivity directly between the cerebellum and subcortical areas involved in reactive aggression does not exclude the possibility of an indirect regulatory pathway via cortical regions. A prefrontal connection could mediate the cerebello-subcortical connection in veterans with aggression symptoms. This is supported by Varkevisser et al. (2017), who reported reduced frontal-subcortical connectivity in a larger sample of veterans, as well as by the present finding of reduced cerebello-frontal connectivity.

Our exploratory analyses found evidence for reduced DCN-OFC functional connectivity in veterans with aggression symptoms in comparison to control veterans. This result adds to the idea for a role of the cerebellum in the frontal-subcortical aggression circuit (Klaus and Schutter, 2021; Kruithof et al., 2022; Wolfs et al., 2022). The OFC is implicated in the encoding of emotional and motivational values (Raine and Yang, 2006; Rosell and Siever, 2015) through reciprocal connections with the amygdala (Blair, 2016; Viviani, 2014; Winstanley et al., 2004). The OFC may thus play a regulatory role in relaying signals that can both decrease and increase the probability of reactive aggression as a result of environmental cues associated with, for example, rewards and threats (Blair, 2004). In agreement with this idea, decreased functional connectivity between the OFC and amygdala has been reported in patients with intermittent explosive disorder (Coccaro et al., 2007). More specifically, it has been proposed that blunted medial prefrontal cortex activity can lead to more aggressive behaviour through a reduced ability to evaluate action-outcome relationships (Blair, 2007). As noted earlier, the lower cerebello-orbitofrontal connectivity observed in the present study is in line with reported lower cerebello-frontal coupling in Tourette disorder patients with rage attacks (Atkinson-Clement et al., 2020). Additionally, reduced cerebello-orbitofrontal functional connectivity has been demonstrated in violent offenders (Leutgeb et al., 2016). A related finding of reduced functional connectivity between left Crus II and left inferior frontal gyrus has also been reported in criminal offenders compared to controls (Amaoui et al., 2022). On a speculative account, reduced cerebello-frontal functional connectivity may contribute to impulsivity and reactive aggression through less cerebellar input to the prefrontal supervisory system (Miquel et al., 2019; Moers-Hornikx et al., 2009). In terms of feedforward models, the cerebellum may be involved in providing information to the prefrontal cortex about response-outcome associations which is used by the OFC during response selection and outcome anticipation (Pisotta and Molinari, 2014). Lower functional connectivity may perhaps reflect a state of suboptimal information transfer between the DCN and OFC. As a result, limited access by the OFC to cerebellar information could potentially predispose individuals to more reactive and inappropriate forms of behaviour. Furthermore, reduced cerebellar input may play a role in decreased prefrontal regulation of limbic areas as indexed by reduced fronto-subcortical connectivity in aggression (Coccaro et al., 2007; Sukhodolsky et al., 2021; Varkevisser et al., 2017). In this context, altered communication between the sensorimotor regions of the cerebellum associated with emotion reactivity and the medial frontal network involved in cognitive control has been found to be predictive of aggressive behaviour in children (Ibrahim et al., 2022). Even though the exact mechanisms remain to be elucidated, our preliminary finding concurs with the growing body of empirical evidence on the involvement of the cerebellum in emotion regulation and impulse control (Adamaszek et al., 2017; Klaus and Schutter, 2021; Schutter, 2020; Wolfs et al., 2022). Future research, with increased field strength and resolution to avoid signal loss in neighbouring structures as well as a larger sample size, is necessary to warrant the functional relations between the cerebellum and subcortical structures.

Limitations of this study include the absence of resting-state fMRI signal in the cerebellar hemispheres and the relatively low resolution of the functional images. Our study focused on the DCN, but future studies on functional connectivity of the cerebellar cortex could provide a more

specific topography of the cerebellum in the core aggression circuit. We assessed relatively small brain structures with average resolution (~3–4 mm^3) and through averaging over neighbouring structures may have failed to detect region-specific group differences. Increasing the signal-to-noise ratio by using high (7T) MR fields and specific cerebellum coils may be beneficial for increasing the specificity and sensitivity (Priovoulos et al., 2021) of associations between cerebellar functional connectivity and behavioural indices of human aggression. Future task-based functional connectivity studies on aggressive behaviour (e.g., Ibrahim et al., 2022) with a more explicit focus on the cerebellum could provide complementary information. Finally, due to the preliminary nature of our study, future systematic research is needed to replicate and further examine the observed reduction in DCN-OFC functional connectivity in veterans with aggressive symptoms and to test whether our current findings in males generalize to the female population. Despite these shortcomings, our preliminary findings hint to the importance of the cerebellum as part of the neural circuitry underlying aggression.

In conclusion, our findings provide the first preliminary evidence for the presence of aberrant cerebello-orbitofrontal functional connectivity in veterans displaying reactive aggression symptoms. The growing body of empirical evidence further strengthens the role of the cerebellum in aggression and is suggestive for a complementary role of the cerebellum to the well-established cortico-limbic theories of emotion regulation.

CRediT author statement

Elze Wolfs: Conceptualization; Methodology; Formal analysis; Writing – original draft and preparation; **Remko van Lutterveld**: Methodology; Writing – review and editing; **Tim Varkevisser**: Methodology; Writing – review and editing; **Jana Klaus**: Conceptualization; Writing – review and editing; Supervision. **Elbert Geuze**: Writing – review and editing; Resources; Funding acquisition. **Dennis Schutter**: Conceptualization; Writing – review and editing; Supervision; Funding acquisition.

Funding

This work was supported by Dutch Ministry of Defence and the Dutch Research Foundation (NWO, VI.C.181.005).

Declaration of competing interest

The authors have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2023.01.023.

References

Abdallah, M., Farrugia, N., Chirokoff, V., Chanraud, S., 2020. Static and dynamic aspects of cerebro-cerebellar functional connectivity are associated with self-reported measures of impulsivity: a resting-state fMRI study. Network Neurosci. 4 (3), 891–909. https://doi.org/10.1162/netn_a_00149.

Adamaszek, M., D'Agata, F., Ferrucci, R., Habas, C., Keulen, S., Kirkby, K.C., Verhoeven, J., 2017. Consensus paper: cerebellum and emotion. Cerebellum 16 (2), 552–576. https://doi.org/10.1007/s12311-016-0815-8.

Allen, G.I., Tsukahara, N., 1974. Cerebrocerebellar communication systems. Physiol. Rev. 54 (4), 957–1006. https://doi.org/10.1152/physrev.1974.54.4.957.

Amaoui, S., Marín-Morales, A., Martín-Pérez, C., Pérez-García, M., Verdejo-Román, J., 2022. Social mentalizing in male perpetrators of intimate partner violence against women is associated with resting-state functional connectivity of the Crus II. J. Psychiatr. Res. 150, 264–271. https://doi.org/10.1016/j.jpsychires.2022.03.044.

Amunts, K., Kedo, O., Kindler, M., Pieperhoff, P., Mohlberg, H., Shah, N.J., Zilles, K., 2005. Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. Anat. Embryol. 210 (5), 343–352. https://doi.org/10.1007/s00429-005-0025-5.

Andersson, J.L., Jenkinson, M., Smith, S., 2007. Non-linear registration, aka Spatial normalisation FMRIB technical report TR07JA2. FMRIB Anal. Group Univ. Oxford. 2 (1), e21.

Atkinson-Clement, C., Sofia, F., Fernandez-Egea, E., de Liege, A., Beranger, B., Klein, Y., Worbe, Y., 2020. Structural and functional abnormalities within sensori-motor and limbic networks underpin intermittent explosive symptoms in Tourette disorder. J. Psychiatr. Res. 125, 1–6. https://doi.org/10.1016/j.jpsychires.2020.02.033.

Baroncini, M., Jissendi, P., Balland, E., Besson, P., Pruvo, J.-P., Francke, J.-P., Prevot, V., 2012. MRI atlas of the human hypothalamus. Neuroimage 59 (1), 168–180. https://doi.org/10.1016/j.neuroimage.2011.07.013.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. Roy. Stat. Soc. B 57 (1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x.

Berman, A., Berman, D., Prescott, J., 1974. The effect of cerebellar lesions on emotional behavior in the rhesus monkey. In: The Cerebellum, Epilepsy, and Behavior. Springer, pp. 277–284.

Blair, R.J.R., 2004. The roles of orbital frontal cortex in the modulation of antisocial behavior. Brain Cognit. 55 (1), 198–208. https://doi.org/10.1016/S0278-2626(03)00276-8.

Blair, R.J.R., 2007. The amygdala and ventromedial prefrontal cortex in morality and psychopathy. Trends Cognit. Sci. 11 (9), 387–392. https://doi.org/10.1016/j.tics.2007.07.003.

Blair, R.J.R., 2016. The neurobiology of impulsive aggression. J. Child Adolesc. Psychopharmacol. 26 (1), 4–9. https://doi.org/10.1089/cap.2015.0088.

Buckner, R.L., Krienen, F.M., Castellanos, A., Diaz, J.C., Yeo, B.T.T., 2011. The organization of the human cerebellum estimated by intrinsic functional connectivity. J. Neurophysiol. 106 (5), 2322–2345. https://doi.org/10.1152/jn.00339.2011.

Buss, A.H., Perry, M., 1992. The aggression questionnaire. J. Pers. Soc. Psychol. 63 (3), 452–459. https://doi.org/10.1037//0022-3514.63.3.452.

Byrge, L., Kennedy, D.P., 2018. Identifying and characterizing systematic temporally-lagged BOLD artifacts. NeuroImage 171, 376–392. https://doi.org/10.1016/j.neuroimage.2017.12.082.

Bzdok, D., Laird, A.R., Zilles, K., Fox, P.T., Eickhoff, S.B., 2013. An investigation of the structural, connectional, and functional subspecialization in the human amygdala. Hum. Brain Mapp. 34 (12), 3247–3266. https://doi.org/10.1002/hbm.22138.

Chen, X., Lu, B., Yan, C.-G., 2018. Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. Hum. Brain Mapp. 39 (1), 300–318. https://doi.org/10.1002/hbm.23843.

Ciric, R., Rosen, A.F.G., Erus, G., Cieslak, M., Adebimpe, A., Cook, P.A., Satterthwaite, T. D., 2018. Mitigating head motion artifact in functional connectivity MRI. Nat. Protoc. 13 (12), 2801–2826. https://doi.org/10.1038/s41596-018-0065-y.

Coccaro, E.F., 2011. Intermittent explosive disorder: development of integrated research criteria for Diagnostic and Statistical Manual of Mental Disorders. In: Comprehensive Psychiatry, fifth ed., pp. 119–125. https://doi.org/10.1016/j.comppsych.2010.05.006 52(2).

Coccaro, E.F., 2012. Intermittent explosive disorder as a disorder of impulsive aggression for DSM-5. Am. J. Psychiatr. 169 (6), 577–588. https://doi.org/10.1176/appi.ajp.2012.11081259.

Coccaro, E.F., McCloskey, M.S., Fitzgerald, D.A., Phan, K.L., 2007. Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol. Psychiatr. 62 (2), 168–178. https://doi.org/10.1016/j.biopsych.2006.08.024.

Conte, G., Valente, F., Fioriello, F., Cardona, F., 2020. Rage attacks in tourette syndrome and chronic tic disorder: a systematic review. Neurosci. Biobehav. Rev. 119, 21–36. https://doi.org/10.1016/j.neubiorev.2020.09.019.

Dark, H.E., Harnett, N.G., Goodman, A.M., Wheelock, M.D., Mrug, S., Schuster, M.A., Knight, D.C., 2020. Violence exposure, affective style, and stress-induced changes in resting state functional connectivity. Cognit. Affect Behav. Neurosci. 20 (6), 1261–1277. https://doi.org/10.3758/s13415-020-00833-1.

Davidson, R.J., Putnam, K.M., Larson, C.L., 2000. Dysfunction in the neural circuitry of emotion regulation–a possible prelude to violence. Science 289 (5479), 591–594. https://doi.org/10.1126/science.289.5479.591.

de Beurs, E., den Hollander-Gijsman, M.E., Helmich, S., Zitman, F.G., 2007. The tripartite model for assessing symptoms of anxiety and depression: psychometrics of the Dutch version of the mood and anxiety symptoms questionnaire. Behav. Res. Ther. 45 (7), 1609–1617. https://doi.org/10.1016/j.brat.2006.07.004.

Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25 (4), 1325–1335. https://doi.org/10.1016/j.neuroimage.2004.12.034.

Esteban Masferrer, M., Silva, B.A., Nomoto, K., Lima, S.Q., Gross, C.T., 2020. Differential encoding of predator fear in the ventromedial hypothalamus and periaqueductal grey. J. Neurosci. 40 (48), 9283–9292. https://doi.org/10.1523/jneurosci.0761-18.2020.

Griffanti, L., Douaud, G., Bijsterbosch, J., Evangelisti, S., Alfaro-Almagro, F., Glasser, M. F., Smith, S.M., 2017. Hand classification of fMRI ICA noise components. Neuroimage 154, 188–205. https://doi.org/10.1016/j.neuroimage.2016.12.036.

Guell, X., D'Mello, A.M., Hubbard, N.A., Romeo, R.R., Gabrieli, J.D.E., Whitfield-Gabrieli, S., Anteraper, S.A., 2019. Functional territories of human dentate nucleus. Cerebr. Cortex 30 (4), 2401–2417. https://doi.org/10.1093/cercor/bhz247.

Habas, C., 2021. Functional connectivity of the cognitive cerebellum. Front. Syst. Neurosci. 15 https://doi.org/10.3389/fnsys.2021.642225.

Habas, C., van Dun, K., Manto, M., Mariën, P., 2016. Chapter 13 - deep cerebellar nuclei (DCN) and language. In: Mariën, P., Manto, M. (Eds.), The Linguistic Cerebellum. Academic Press, San Diego, pp. 337–353.

Habas, C., Kamdar, N., Nguyen, D., Prater, K., Beckmann, C.F., Menon, V., Greicius, M. D., 2009. Distinct cerebellar contributions to intrinsic connectivity networks. J. Neurosci. 29 (26), 8586–8594. https://doi.org/10.1523/jneurosci.1868-09.2009.
Heath, R.G., 1977. Modulation of emotion with a brain pacemaker: treatment for intractable psychiatric illness. J. Nerv. Ment. Dis. 165 (5), 300–317. https://doi.org/10.1097/00005053-197711000-00002.
Heath, R.G., Llewellyn, R.C., Rouchell, A.M., 1980. The cerebellar pacemaker for intractable behavioral disorders and epilepsy: follow-up report. Biol. Psychiatr. 15 (2), 243–256.
Hovens, J., Lievaart, M., Rodenburg, J., 2014. STAXI-2: Vragenlijst over Boosheid. Hogrefe, Amsterdam.
Ibrahim, K., Noble, S., He, G., Lacadie, C., Crowley, M.J., McCarthy, G., Sukhodolsky, D. G., 2022. Large-scale functional brain networks of maladaptive childhood aggression identified by connectome-based predictive modeling. Mol. Psychiatr. 27 (2), 985–999. https://doi.org/10.1038/s41380-021-01317-5.
Jackman, S.L., Chen, C.H., Offermann, H.L., Drew, I.R., Harrison, B.M., Bowman, A.M., Regehr, W.G., 2020. Cerebellar Purkinje cell activity modulates aggressive behavior. Elife 9, e53229. https://doi.org/10.7554/eLife.53229.
Jenkinson, M., Bannister, P., Brady, M., Smith, S., 2002. Improved optimization for the robust and accurate linear registration and motion correction of brain images. Neuroimage 17 (2), 825–841. https://doi.org/10.1006/nimg.2002.1132.
Jenkinson, M., Beckmann, C.F., Behrens, T.E.J., Woolrich, M.W., Smith, S.M., 2012. FSL. NeuroImage 62 (2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015.
Jenkinson, M., Smith, S., 2001. A global optimisation method for robust affine registration of brain images. Med. Image Anal. 5 (2), 143–156. https://doi.org/10.1016/S1361-8415(01)00036-6.
Klaus, J., Schutter, D.J.L.G., 2021. Functional topography of anger and aggression in the human cerebellum. Neuroimage 226, 117582. https://doi.org/10.1016/j.neuroimage.2020.117582.
Kruithof, E.S., Klaus, J., Schutter, D.J.L.G., 2022. The cerebellum in aggression: extending the cortico-limbic dual-route model of motivation and emotion. Motivation Sci. 8 (2), 150–160. https://doi.org/10.1037/mot0000251.
Krzywkowski, P., Penna, B., Gross, C.T., 2020. Dynamic encoding of social threat and spatial context in the hypothalamus. Elife 9, e57148. https://doi.org/10.7554/eLife.57148.
Kullmann, S., Heni, M., Linder, K., Zipfel, S., Häring, H.-U., Veit, R., Preissl, H., 2014. Resting-state functional connectivity of the human hypothalamus. Hum. Brain Mapp. 35 (12), 6088–6096. https://doi.org/10.1002/hbm.22607.
Leutgeb, V., Wabnegger, A., Leitner, M., Zussner, T., Scharmüller, W., Klug, D., Schienle, A., 2016. Altered cerebellar-amygdala connectivity in violent offenders: a resting-state fMRI study. Neurosci. Lett. 610, 160–164. https://doi.org/10.1016/j.neulet.2015.10.063.
Levisohn, L., Cronin-Golomb, A., Schmahmann, J.D., 2000. Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123 (5), 1041–1050. https://doi.org/10.1093/brain/123.5.1041.
Linnman, C., Moulton, E.A., Barmettler, G., Becerra, L., Borsook, D., 2012. Neuroimaging of the periaqueductal gray: state of the field. Neuroimage 60 (1), 505–522. https://doi.org/10.1016/j.neuroimage.2011.11.095.
Lischinsky, J.E., Lin, D., 2020. Neural mechanisms of aggression across species. Nat. Neurosci. 23 (11), 1317–1328. https://doi.org/10.1038/s41593-020-00715-2.
MacManus, D., Rona, R., Dickson, H., Somaini, G., Fear, N., Wessely, S., 2015. Aggressive and violent behavior among military personnel deployed to Iraq and Afghanistan: prevalence and link with deployment and combat exposure. Epidemiol. Rev. 37 (1), 196–212. https://doi.org/10.1093/epirev/mxu006.
Marek, S., Greene, D.J., 2021. Precision functional mapping of the subcortex and cerebellum. Curr. Opinion. Behave Sci. 40, 12–18. https://doi.org/10.1016/j.cobeha.2020.12.011.
Meesters, C., Muris, P., Bosma, H., Schouten, E., Beuving, S., 1996. Psychometric evaluation of the Dutch version of the aggression questionnaire. Behav. Res. Ther. 34 (10), 839–843. https://doi.org/10.1016/0005-7967(96)00065-4.
Miles, S.R., Sharp, C., Tharp, A.T., Stanford, M.S., Stanley, M., Thompson, K.E., Kent, T. A., 2017. Emotion dysregulation as an underlying mechanism of impulsive aggression: reviewing empirical data to inform treatments for veterans who perpetrate violence. Aggress. Violent Behav. 34, 147–153. https://doi.org/10.1016/j.avb.2017.01.017.
Miquel, M., Nicola, S.M., Gil-Miravet, I., Guarque-Chabrera, J., Sanchez-Hernandez, A., 2019. A working hypothesis for the role of the cerebellum in impulsivity and compulsivity. Front. Behav. Neurosci. 13 (99) https://doi.org/10.3389/fnbeh.2019.00099.
Moers-Hornikx, V.M.P., Sesia, T., Basar, K., Lim, L.W., Hoogland, G., Steinbusch, H.W. M., Vles, J.S.H., 2009. Cerebellar nuclei are involved in impulsive behaviour. Behav. Brain Res. 203 (2), 256–263. https://doi.org/10.1016/j.bbr.2009.05.011.
Öhman, A., 2005. The role of the amygdala in human fear: automatic detection of threat. Psychoneuroendocrinology 30 (10), 953–958. https://doi.org/10.1016/j.psyneuen.2005.03.019.
Orth, U., Wieland, E., 2006. Anger, hostility, and posttraumatic stress disorder in trauma-exposed adults: a meta-analysis. J. Consult. Clin. Psychol. 74 (4), 698. https://doi.org/10.1037/0022-006X.74.4.698.
Panksepp, J., Biven, L., 2012. Chapter 4: the ancestral sources of rage. In: The Archaeology of Mind: Neuroevolutionary Origins of Human Emotion. W. W. Norton & Company, New York, NY, US.
Paret, C., Ruf, M., Gerchen, M.F., Kluetsch, R., Demirakca, T., Jungkunz, M., Ende, G., 2016. fMRI neurofeedback of amygdala response to aversive stimuli enhances prefrontal–limbic brain connectivity. Neuroimage 125, 182–188. https://doi.org/10.1016/j.neuroimage.2015.10.027.
Pisotta, I., Molinari, M., 2014. Cerebellar contribution to feedforward control of locomotion. Front. Hum. Neurosci. 8 https://doi.org/10.3389/fnhum.2014.00475, 475-475.
Priovoulos, N., Roos, T., Ipek, Ö., Meliado, E.F., Nkrumah, R.O., Klomp, D.W.J., van der Zwaag, W., 2021. A local multi-transmit coil combined with a high-density receive array for cerebellar fMRI at 7 T. NMR Biomed. 34 (11), e4586 https://doi.org/10.1002/nbm.4586.
Pruim, R.H., Mennes, M., van Rooij, D., Llera, A., Buitelaar, J.K., Beckmann, C.F., 2015. ICA-AROMA: a robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage 112, 267–277. https://doi.org/10.1016/j.neuroimage.2015.02.064.
Raine, A., Yang, Y., 2006. Neural foundations to moral reasoning and antisocial behavior. Soc. Cognit. Affect Neurosci. 1 (3), 203–213. https://doi.org/10.1093/scan/nsl033.
Reijnen, A., Rademaker, A.R., Vermetten, E., Geuze, E., 2015. Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. Eur. Psychiatr. 30 (2), 341–346. https://doi.org/10.1016/j.eurpsy.2014.05.003.
Reis, D.J., Doba, N., Nathan, M.A., 1973. Predatory attack, grooming, and consummatory behaviors evoked by electrical stimulation of cat cerebellar nuclei. Science 182 (4114), 845–847. https://doi.org/10.1126/science.182.4114.845.
Rosell, D.R., Siever, L.J., 2015. The neurobiology of aggression and violence. CNS Spectr. 20 (3), 254–279. https://doi.org/10.1017/S109285291500019X.
Roy, A.K., Benson, B.E., Degnan, K.A., Perez-Edgar, K., Pine, D.S., Fox, N.A., Ernst, M., 2014. Alterations in amygdala functional connectivity reflect early temperament. Biol. Psychol. 103, 248–254. https://doi.org/10.1016/j.biopsycho.2014.09.007.
RStudio Team, 2018. RStudio. Integrated Development for R. RStudio, Inc., Boston, MA. URL. http://www.rstudio.com/.
Schmahmann, J.D., 2019. The cerebellum and cognition. Neurosci. Lett. 688, 62–75. https://doi.org/10.1016/j.neulet.2018.07.005.
Schmahmann, J.D., Doyon, J., Petrides, M., Evans, A.C., Toga, A.W., 2000. MRI Atlas of the Human Cerebellum. Academic press.
Schmahmann, J.D., Sherman, J.C., 1998. The cerebellar cognitive affective syndrome. Brain 121 (4), 561–579. https://doi.org/10.1093/brain/121.4.561.
Schutter, D.J.L.G., 2020. The Cerebellum in Emotions and Psychopathology, first ed. Routledge. https://doi.org/10.4324/9781315145082.
Siever, L.J., 2008. Neurobiology of aggression and violence. Am. J. Psychiatr. 165 (4), 429–442. https://doi.org/10.1176/appi.ajp.2008.07111774.
Singh, K., Cauzzo, S., García-Gomar, M.G., Stauder, M., Vanello, N., Passino, C., Bianciardi, M., 2022. Functional connectome of arousal and motor brainstem nuclei in living humans by 7 Tesla resting-state fMRI. Neuroimage 249, 118865. https://doi.org/10.1016/j.neuroimage.2021.118865.
Smith, S.M., 2002. Fast robust automated brain extraction. Hum. Brain Mapp. 17 (3), 143–155. https://doi.org/10.1002/hbm.10062.
Spielberger, C.D., Sydeman, S.J., Owen, A.E., Marsh, B.J., 1999. Measuring Anxiety and Anger with the State-Trait Anxiety Inventory (STAI) and the State-Trait Anger Expression Inventory (STAXI). Lawrence Erlbaum Associates Publishers.
Sukhodolsky, D.G., Ibrahim, K., Kalvin, C.B., Jordan, R.P., Eilbott, J., Hampson, M., 2021. Increased amygdala and decreased frontolimbic resting-state functional connectivity in children with aggressive behavior. Soc. Cognit. Affect Neurosci. https://doi.org/10.1093/scan/nsab128.
Terburg, D., Scheggia, D., Triana del Rio, R., Klumpers, F., Ciobanu, A.C., Morgan, B., van Honk, J., 2018. The basolateral amygdala is essential for rapid escape: a human and rodent study. Cell 175 (3), 723–735. https://doi.org/10.1016/j.cell.2018.09.028 e716.
Tessier, A., Cosin, C., Mayo, W., Pfeuty, M., Misdrahi, D., Sibon, I., 2015. Impulsive aggressive obsessions following cerebellar strokes: a case study. J. Neurol. 262 (7), 1775–1776. https://doi.org/10.1007/s00415-015-7804-6.
Tonna, M., Ottoni, R., Ossola, P., De Panfilis, C., Marchesi, C., 2014. Late-onset obsessive-compulsive disorder associated with left cerebellar lesion. Cerebellum 13 (4), 531–535. https://doi.org/10.1007/s12311-014-0561-8.
van den Heuvel, M.P., Hulshoff Pol, H.E., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol 20 (8), 519–534. https://doi.org/10.1016/j.euroneuro.2010.03.008.
van Lutterveld, R., Varkevisser, T., Kouwer, K., van Rooij, S.J.H., Kennis, M., Hueting, M., Geuze, E., 2022. Spontaneous brain activity, graph metrics, and head motion related to prospective post-traumatic stress disorder trauma-focused therapy response. Front. Hum. Neurosci. 16, 730745 https://doi.org/10.3389/fnhum.2022.730745.
Varkevisser, T., Gladwin, T.E., Heesink, L., van Honk, J., Geuze, E., 2017. Resting-state functional connectivity in combat veterans suffering from impulsive aggression. Soc. Cognit. Affect Neurosci. 12 (12), 1881–1889. https://doi.org/10.1093/scan/nsx113.
Viviani, R., 2014. Neural correlates of emotion regulation in the ventral prefrontal cortex and the encoding of subjective value and economic utility. Front. Psychiatr. 5 https://doi.org/10.3389/fpsyt.2014.00123, 123-123.
Watson, D., Clark, L.A., 1991. Mood and anxiety symptom questionnaire. J. Behav. Ther. Exp. Psychiatr. https://doi.org/10.1037/t13679-000.
Winstanley, C.A., Theobald, D.E.H., Cardinal, R.N., Robbins, T.W., 2004. Contrasting roles of basolateral amygdala and orbitofrontal cortex in impulsive choice. J. Neurosci. 24 (20), 4718–4722. https://doi.org/10.1523/jneurosci.5606-03.2004.
Wolfs, E.M.L., Klaus, J., Schutter, D.J.L.G., 2022. Cerebellar grey matter volumes in reactive aggression and impulsivity in healthy volunteers. Cerebellum. https://doi.org/10.1007/s12311-021-01337-5.
Woolrich, M.W., Behrens, T.E.J., Beckmann, C.F., Jenkinson, M., Smith, S.M., 2004. Multilevel linear modelling for FMRI group analysis using Bayesian inference.

Neuroimage 21 (4), 1732–1747. https://doi.org/10.1016/j.neuroimage.2003.12.023.
Woolrich, M.W., Ripley, B.D., Brady, M., Smith, S.M., 2001. Temporal autocorrelation in univariate linear modeling of FMRI data. Neuroimage 14 (6), 1370–1386. https://doi.org/10.1006/nimg.2001.0931.
Worsley, K.J., 2001. Statistical analysis of activation images. Functional MRI: Intro. Method. 14 (1), 251–270.
Xu, T., Zhao, Q., Wang, P., Fan, Q., Chen, J., Zhang, H., Wang, Z., 2019. Altered resting-state cerebellar-cerebral functional connectivity in obsessive-compulsive disorder. Psychol. Med. 49 (7), 1156–1165. https://doi.org/10.1017/S0033291718001915.
Yarkoni, T., Poldrack, R.A., Nichols, T.E., Van Essen, D.C., Wager, T.D., 2011. Large-scale automated synthesis of human functional neuroimaging data. Nat. Methods 8 (8), 665–670. https://doi.org/10.1038/nmeth.1635.
Zanchetti, A., Zoccolini, A., 1954. Autonomic hypothalamic outbursts elicited by cerebellar stimulation. J. Neurophysiol. 17 (5), 475–483. https://doi.org/10.1152/jn.1954.17.5.475.