Brain Struct Funct (2016) 221:3081–3093
DOI 10.1007/s00429-015-1088-6

ORIGINAL ARTICLE

Individual differences in resting-state functional connectivity with the executive network: support for a cerebellar role in anxiety vulnerability

Meghan D. Caulfield[1,2,3] · **David C. Zhu**[4,5] · **J. Devin McAuley**[1,5] · **Richard J. Servatius**[1,2,6]

Received: 3 April 2014 / Accepted: 16 July 2015 / Published online: 1 August 2015

Abstract This study characterized cerebellar connectivity with executive intrinsic functional connectivity networks. Using seed regions at the right and left dorsolateral prefrontal cortices (dlPFC) and right orbital frontoinsula, we measured resting-state brain connectivity in healthy college-aged participants. Based on the previous research demonstrating a relationship between the cerebellum and self-report measures of behavioral inhibition, we assessed individual differences in connectivity between groups. Overall, intrinsic activity in cerebellar lobule VIII was significantly correlated with the executive network and cerebellar Crus I with the salience network. Between-group comparisons indicated stronger cerebellar connectivity with the executive network in behaviorally inhibited individuals. Intrinsic activity in Crus I, a region previously implicated in non-motor cerebellar functions, significantly correlated with intrinsic activity in the right dlPFC seed region. These findings support a growing number of studies demonstrating cerebellar influence on higher cognitive processes, extending this relationship to individual differences in anxiety vulnerability.

Keywords Cerebellum · Anxiety vulnerability · Executive network · Resting-state functional connectivity · Behavioral inhibition

Introduction

The cerebellum is traditionally thought of as a motor structure. However, awareness that the cerebellum plays a role in higher cognitive functions is growing. Evidence from anatomical studies in primates (Kelly and Strick 2003; Middleton and Strick 2001) and clinical work in humans (Nashold and Slaughter 1969; Heath et al. 1974; Cooper et al. 1976; Schmahmann 1991; Schmahmann et al. 2009) supports a growing number of imaging studies reporting cerebellar activity that is not linked to motor behavior, such as emotion, attention, and social cognition (Liddle et al. 2001; Schall et al. 2003; Blackwood et al. 2004; Lee et al. 2004; Habel et al. 2005; Bermpohl et al. 2006; Hofer et al. 2007; Van Overwalle et al. 2014).

The cerebellum has widespread connections to both motor regions of the primary and premotor cortex and non-motor regions including prefrontal areas (Glickstein et al. 1985; Kelly and Strick 2003; Clower et al. 2005). Detailed anatomical studies indicate a discrete topography organizing cerebellar input and output to cortical areas (Schmahmann and Pandya 1997; Dum and Strick 2002). Using tract-tracing methods in primates, Strick and colleagues demonstrate that non-motor regions of the prefrontal cortex (Brodmann areas 9 and 46) have distinct connections to the dentate nucleus of the cerebellum (Middleton and Strick 2001; Dum and Strick 2002).

✉ Meghan D. Caulfield
mcaulfield@kesslerfoundation.org

[1] Stress and Motivated Behavior Institute, East Orange, NJ, USA

[2] Graduate School of Biomedical Sciences, Rutgers University, Newark, NJ, USA

[3] Kessler Foundation, West Orange, NJ, USA

[4] Department of Radiology, Michigan State University, East Lansing, MI, USA

[5] Department of Psychology, Michigan State University, East Lansing, MI, USA

[6] Department of Veterans Affairs, Veterans Affairs Medical Center, Syracuse, NY, USA

Critically, they demonstrated that the ventral dentate nucleus projects to the prefrontal cortex (PFC), with separate dorsal dentate projections terminating in the motor and premotor regions, indicating a topographic organization of the dentate nucleus supporting both motor and non-motor output to the cortex (Dum and Strick 2002). These results have led to the proposal that the cortico-cerebellar connections are via reciprocal "parallel circuits" that connect the cerebellum to the cortical regions, and vice versa (Bostan et al. 2013).

Cerebellar connectivity to non-motor areas is also supported by recent research using resting-state functional magnetic resonance (fMRI) imaging techniques. Resting-state fMRI is based on the theory that fluctuating brain activity at rest correlates between brain regions, reflecting intrinsic functional networks of the brain (Biswal et al. 1995; Fox and Raichle 2007). For example, regions typically associated with motor function tend to activate in synchrony, waxing and waning together, and are therefore considered to form a particular network (Beckmann et al. 2005; Seeley et al. 2007). Studies have demonstrated intrinsic connectivity networks (ICNs) corresponding to basic neural functions such as sensorimotor, vision, audition, language, executive function and salience detection (Xiong et al. 1999; Cordes et al. 2000; Greicius et al. 2003; Kiviniemi et al. 2003; Beckmann et al. 2005; Fox et al. 2005; Fransson 2005; Seeley et al. 2007). Recent work analyzing subcortical contributions to the ICNs has paid little attention to cerebellar connectivity. Those studies that have assessed cerebellar connectivity with the ICNs have been promising, demonstrating cerebellar contributions to all functional networks (Habas et al. 2009). Importantly, these studies have shown that regions of the cerebellum contribute distinctly to individual networks, with some regions such as cerebellar Crus I, Crus II and lobule VI contributing specifically to cortical networks such as the executive control and salience networks (Habas et al. 2009; O'Reilly et al. 2010; Bucker et al. 2011; Bernard et al. 2012).

Resting-state fMRI provides a useful platform to study individual differences in connectivity in both clinical and non-clinical populations. So far, anxiety researchers have primarily considered the possibility of intrinsic connectivity differences in psychopathology, such as individuals with social anxiety disorder (Liao et al. 2010a, b; Ding et al. 2011; Hahn et al. 2011; Anteraper et al. 2014), obsessive compulsive disorder (Jang et al. 2010) and post-traumatic stress disorder (PTSD; Bonne et al. 2003; Gilboa et al. 2004; Bluhm et al. 2009; Lanius et al. 2010; Rabinak et al. 2011; Sripada et al. 2012). However, individual differences in intrinsic connectivity may be a pre-existing risk factor for the development of an anxiety disorder. For example, a stress-diathesis approach suggests that anxiety is due to the interaction of risk factors such as sex, genetics, personality (Mineka and Zinbarg 2006), brain structure (Gilbertson et al. 2002) and learning (Caulfield et al. 2013; Holloway et al. 2013; Caulfield et al. 2015). It is likely that connectivity may also play an essential role in mediating risk for developing clinical anxiety.

Recent research supports a diathesis approach to understanding anxiety vulnerability. Individual differences in learning performance were found on a cerebellar-mediated associative learning task (Caulfield et al. 2013, 2015). In this task, participants were given a battery of measures related to risk for anxiety including the Adult Measure of Behavioral Inhibition (AMBI; Gladstone and Parker 2005), a measure of behavioral inhibition that has been linked to greater risk for developing clinical anxiety (Biederman et al. 1990; Hirshfeld et al. 1992; Biederman et al. 2001; Schwartz et al. 2012), and then underwent eyeblink classical conditioning. Those with high scores on the AMBI learned significantly faster than those with low scores, suggesting that there is something fundamentally different about how those at risk for an anxiety disorder learn about their environments. However, aside from a handful of electroencephalography studies (Knyazev 2007; Putman 2011) no studies to date have assessed individual differences in intrinsic connectivity of behaviorally inhibited individuals using resting-state fMRI.

It remains unclear why those with behaviorally inhibited temperament demonstrate individual differences in eyeblink conditioning (Caulfield et al. 2013; Caulfield et al. 2015), as well as enhanced avoidance learning (Sheynin et al. 2013). Reciprocal connectivity between the cerebellum and cortical regions places it in a position to modulate higher cognitive processes via connections with the dorsolateral prefrontal cortex (dlPFC). In addition to its role as a major structure in the executive ICN (Seeley et al. 2007; E et al. 2014), the dlPFC also plays an important role in many executive functions including approach and avoidance motivation (Spielberg et al. 2011, 2012).

The present study had two purposes. The first was to further delineate the role of the cerebellum in specific non-motor ICNs. The second was to assess individual differences in connectivity with intrinsic connectivity networks implicated in anxiety vulnerability. Given the behavioral profile observed in behavioral inhibition, the executive network and salience network are the most likely candidates to demonstrate individual differences. As such, recent research studies have reported increased resting-state connectivity of the amygdala and insula in Veterans with PTSD, implicating the salience network (Sripada et al. 2012). However, given previous research in cerebellar-mediated eyeblink conditioning (Caulfield et al. 2013, 2015), avoidance learning (Sheynin et al. 2013), and task-based fMRI (Blackford et al. 2009), we hypothesized that regions in the cerebellum will significantly correlate with executive network resting-state fluctuations, with inhibited individuals demonstrating greater cerebellar connectivity with the executive network.

Materials and methods

Participants

Twenty-six young adults ($n = 19$ female, $n = 7$ male), ages 18–25 ($M = 20.7$, SD = 1.8), from a large midwestern university participated in the study. All study materials were reviewed and approved by internal review board and informed consent was obtained from all participants prior to any experimental procedures.

Psychometric scales

Participants completed a battery of self-report measures including the Adult and Retrospective Measures of Behavioral Inhibition (Gladstone and Parker 2005) and the Spielberger State/Trait Anxiety Inventory (Spielberger et al. 1983). Participants were part of a larger study on behavioral inhibition and as such were classified as behaviorally inhibited if their AMBI score was above the median of 11 and non-inhibited if they scored below the median (Caulfield et al. 2013). Except for AMBI score, there were no significant differences between group demographics, all t's > 0.603, see Table 1.

The Adult Measure of Behavioral Inhibition is a 16-item self-report measure that assesses inhibition or avoidance in response to new stimuli or social situations. Scores range from 0 to 32 and include questions such as “Do you tend to withdraw and retreat from those around you?” and “Do you tend to introduce yourself to new people?” (Gladstone and Parker 2005). The Spielberger State/Trait Anxiety Inventory (STAI) is a 40-item self-report questionnaire with total scores ranging from 40 to 160. The STAI is separated into two parts, State and Trait anxiety, each consisting of 20 questions: State Anxiety is assumed to change with mood and emotion and asks questions about the current emotional state of the participant such as “I am tense” and “I feel at ease”. Trait Anxiety is a relatively stable personality characteristic and asks questions about general feelings and behaviors such as “I feel nervous and restless” and “I feel satisfied with myself” (Spielberger et al. 1983).

Imaging data acquisition

The MRI experiment was conducted on a GE 3T Signa® HDx MR scanner (GE Healthcare, Waukesha, WI) with an 8-channel head coil. During each session, first and higher-order shimming procedures were carried out to improve magnetic field homogeneity. To study resting-state brain function, a 7-min echo-planar imaging datasets, starting from the most inferior regions of the cerebellum, were acquired with the following parameters: 44 contiguous 3-mm axial slices in an interleaved order, time of echo (TE) = 20 ms, time of repetition (TR) = 2500 ms, parallel acceleration factor = 2, flip angle = 80°, field of view (FOV) = 22 cm, matrix size = 64 × 64, ramp sampling, and with the first four data points discarded. Each volume of slices was acquired 164 times while a subject was asked to relax, stay awake and keep his eyes closed. After the functional data acquisition, 180 T_1-weighted 1-mm^3 isotropic volumetric inversion recovery fast spoiled gradient-recalled images (10 min scan time), with cerebrospinal fluid (CSF) suppressed, were obtained to cover the whole brain with the following parameters: TE = 3.8 ms, TR of acquisition = 8.6 ms, time of inversion (TI) = 831 ms, TR of inversion = 2332 ms, flip angle = 8°, FOV = 25.6 × 25.6 cm, matrix size = 256 × 256, slice thickness = 1 mm, and receiver bandwidth = ±20.8 kHz.

Resting-state fMRI individual-subject data preprocessing

Resting-state fMRI correlation analysis was conducted using AFNI software (Cox 1996) in the native space. For each subject, the acquisition timing difference was first corrected for different slice locations. With the last functional volume as the reference, rigid-body motion correction was done in three translational and three rotational directions. The amount of motion was estimated and then modeled in data analysis. For each subject, spatial blurring with a full width half maximum (FWHM) of 4 mm was used to reduce random noise and inter-subject anatomical variation during group analysis. At each voxel, motion-

Table 1 Group mean demographic details

Group	N	Females (n)	AMBI (SD)	Age (SD)	Education (SD)
High (scores >11.5)	13	10	16.3 (2.4)	20.8 (2.0)	14.8 (2.1)
Low (scores <11.5)	13	9	8.5 (2.1)	20.5 (1.7)	14.5 (1.4)

AMBI adult measure of behavioral inhibition estimation parameters, baseline, linear and quadratic system-induced signal trends were removed from the time courses using the “3dDeconvolve” routine in AFNI (Ward 2000a). Brain global, CSF and white matter (WM) mean signals were modeled as nuisance variables and removed from the time courses as well. To create the time course from pure CSF regions, the lateral and 3rd ventricles on the high-resolution T_1-weighted volumetric images were segmented using FreeSurfer software followed by 1 mm^3 erosion (Fischl et al. 2002). For the same reason, the WM was segmented from the T_1-weighted volumetric images using the “FAST” routine in the FSL software (Smith et al. 2004) followed by $4 \times 4 \times 4$ mm cubical erosion. The cleaned time courses were then band-pass filtered in the range of 0.009–0.08 Hz (Fox et al. 2005). These filtered time courses were used for correlation-based connectivity analyses following.

Generation of seed regions

Previous research indicates that individuals with behavioral inhibition may react differently to novel situations, people, or stimuli (Blackford et al. 2009; Clauss et al. 2015). Based on previous research indicating individual differences in cerebellar-mediated learning tasks (Caulfield et al. 2013, 2015), we chose to concentrate on cerebellar contributions to known cortical networks. First, we examined cerebellar contributions to established sensorimotor networks by examining regions of correlating activity with cortical motor seeds. For comparison with established functional relationships of the cerebellum with the sensorimotor network (Buckner et al. 2011), we placed spherical seeds with radii of 5 mm on the right hand knob ($X = 45$, $Y = -38$, $Z = 62$) and left hand knob ($X = -40$, $Y = -32$, $Z = 59$) for each participant. Additionally, the dorsolateral prefrontal cortical region has been indicated as important in processing novelty in the environment (Berns et al. 1997) as well as in avoidant behaviors (Aupperle and Paulus 2010; Spielberg et al. 2012, 2011). Given the relationship between behavioral inhibition, attention to novelty, and avoidance we chose to place seed regions in the right and left dlPFC, a central structure in the executive network. Spherical seed regions with radii of 6 mm were placed for each participant in the right dlPFC ($x = 42$, $y = 41$ $z = 23$) and left dlPFC ($x = -45$, $y = 44$, $z = 20$) to assess connectivity with the executive network. Additionally, seed regions with 6 mm radii were placed for each participant in the right orbital frontoinsula ($x = 38$, $y = 12$, $z = -8$) to assess connectivity with the salience network (Seeley et al. 2007). Each seed was visually assessed against anatomy and the location was modified if necessary.

Functional Connectivity between executive network seeds and Rest of the Brain

The “3dfim+” routine in AFNI (Cox 1996) was used to correlate the time course in every voxel of the brain against the space-averaged time course from a seed region. To prepare for group analysis, the correlation coefficients were converted to Z values through Fisher’s Z transformation to improve the normality of the distribution. The Z values were then warped to the MNI305 standard space through the FreeSurfer non-linear registration pipeline as done by Zhu et al. (2013). After warping to the MNI305 standard space, the data were spatially blurred with FWHM of 2 mm to reduce potential noise generated by non-linear warping. Between-group t-tests were performed, as well as the whole group vs. baseline. Cerebellar structural and functional data were isolated and normalized into standard stereotaxic space using the spatially unbiased atlas template (SUIT) of the human cerebellum (Diedrichsen 2006; Diedrichsen et al. 2009) in MRIcron (Rorden et al. 2007).

Monte Carlo simulation was performed according to the matrix and voxel size of the imaging volume, voxel intensity thresholding, masking and spatial smoothness of image data inherited and applied. The spatial smoothness of image data was estimated based on “3dFWHMx” in AFNI (Cox 1996). The cluster analysis was used to estimate the overall statistical significance with respect to the whole brain (Ward 2000b). The between-group t-test results for functional connectivity with the seed region were corrected for multiple comparisons based on the following criteria: A voxel was considered significant only if it was within an 1170 mm^3 cluster in which the voxels were connected and all had a voxel-based $p \leq 0.005$. Based on the application of these criteria to the whole brain, the voxel-based $p \leq 0.005$ was corrected to be an equivalent whole-brain corrected $p \leq 0.047$.

Results

Whole group analysis

The results of functional connectivity analyses over all participants are presented in Table 2. In line with expectations, the right and left motor cortex seeds significantly correlated with known regions of the sensorimotor network including activations across the postcentral gyrus, bilateral thalamus, and the cerebellum. Figure 1 demonstrates contralateral correlates of motor cortical seeds in the cerebellum lobules V and VIII replicating the crossed lateralization and double representation reported by Buckner et al. (2011). The right and left dlPFC seed regions showed significantly greater connectivity with a

Table 2 Locations of positively correlating activity with seeded regions of interest

R/L	Brain region (location of maximum intensity)	Max *t* coordinate (*x*, *y*, *z*)	Cluster size (mm^3)	Max *t* value
Left hand seed region				
L	Postcentral gyrus (BA 2)[a]	−40, −32, 59	323259	25.6730
L	Middle occipital gyrus (BA 37)	−44, −64, −9	6250	5.1347
L	Thalamus	−12, −23, 4	3587	10.0510
R	Cerebellum VIIIa/VIIb	23, −49, −67	3319	7.8106
R	Thalamus	9, −23, 4	2875	7.0531
R	Middle occipital gyrus (BA 37)	47, −66, −8	2630	4.7571
L	Brain stem/pons	−9, −18, −37	1816	5.7657
R	Cerebellum V	22, −47, −32	1239	5.3116
Right hand seed region				
R	Postcentral gyrus (BA 2)[a]	45, −38, 62	350213	23.3580
L	Cerebellum VIIIa/VIIIb	−21, −61, −49	6777	7.3973
L	Cerebellum Lobule V	−19, −51, −21	6052	5.8334
R	Thalamus	15, −23, −4	2774	8.9961
L	Thalamus	−11, −20, −1	1874	5.9440
Left dlPFC seed region				
L	Dorsolateral prefrontal cortex (BA 46/10)[a]	−40, 37, 22	145290	19.3530
L	Inferior parietal lobule (BA 40)	−53, −54, 49	16386	7.3034
L	Middle temporal gyrus (BA 20)	−57, −48, −14	8083	6.3015
R	Inferior parietal lobule (BA 40)	44, −57, 49	6151	6.6122
R	Cerebellum VIII/Crus I/Crus II	26, −70, −66	5686	6.5349
R	Middle temporal gyrus (BA 20)	58, −50, −15	3928	6.6377
R	Extrastriate Cortex (18/19)	12, −76, −43	1626	6.2026
Right dlPFC seed region				
R	Dorsolateral prefrontal cortex (BA 46/10)[a]	38, 45, 25	200981	18.8000
R	Inferior parietal lobule (BA 40)	52, −49, 49	22102	11.0190
L	Inferior parietal lobule (BA 40)	−46, −58, 46	7767	6.2433
R	Middle temporal gyrus (BA 37)	54, −52, −9	7351	6.0750
L	Cerebellum VIII	−24, −68, −69	3897	5.4811
R	Precuneus (BA 7/5)	5, −41, 49	1221	5.1153
Right orbital frontoinsula seed region				
R	Insula[a]	40, 7, −6	182692	16.4300
R	Inferior parietal lobule (BA 40)	58, −45, 38	10108	7.4944
L	Inferior parietal lobule (BA 40)	−66, −31, 24	4991	6.1427
L	Cerebellum Crus I	−40, −49, −41	2581	5.5327

BA Brodmann's area, *dlPFC* dorsolateral prefrontal cortex

[a] Cluster includes the seed region

number of cortical and subcortical regions related to executive functioning including the inferior parietal lobules, middle temporal gyrus, and caudate, in line with prior research of executive network regions (Fig. 2a, b; Seeley et al. 2007; Habas et al. 2009). Assessment of negative correlations reveals that right and left dlPFC seeds are anticorrelated with default mode network (DMN) regions (Table 3). Clusters negatively correlating with activity in the right and left dlPFC contained DMN structures including the posterior cingulate cortex, cingulate gyrus, inferior temporal gyrus, and angular gyrus (Fig. 2c, d; Watanabe et al. 2012; Zhu et al. 2013). Furthermore, significant clusters in the cerebellum correlated with activity of these executive network structures including the Crus I,

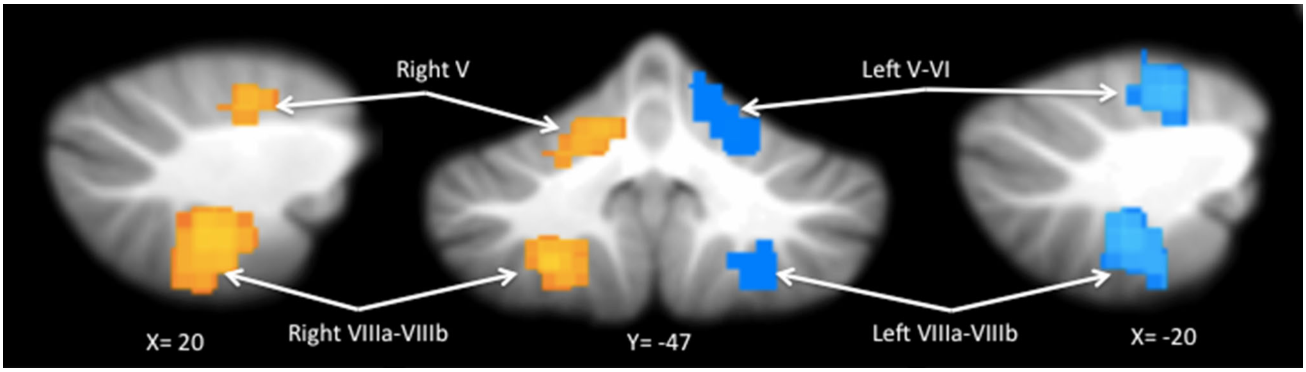

Fig. 1 Functional connectivity of the cortical motor hand region seeds reveals contralateral somatomotor correlates with the cerebellum. Sagittal and coronal sections display functional connectivity between individually placed seeds of the right hand knob region of the motor cortex (approximately $X = 30$, $Y = -30$, $Z = 55$) and the left cerebellum (areas in *blue*) including anterior regions spanning lobules V into VI and posterior lobe locations including lobules VIIIa and VIIIb. The *left* hand knob seed (approximately $X = -30$, $Y = -30$, $Z = 55$) and the *right* cerebellum (areas in *yellow*) showed similar correlating activity, with anterior regions of lobule V and posterior lobe activity in lobules VIIIa and VIIIb. Color bars indicate *t* values

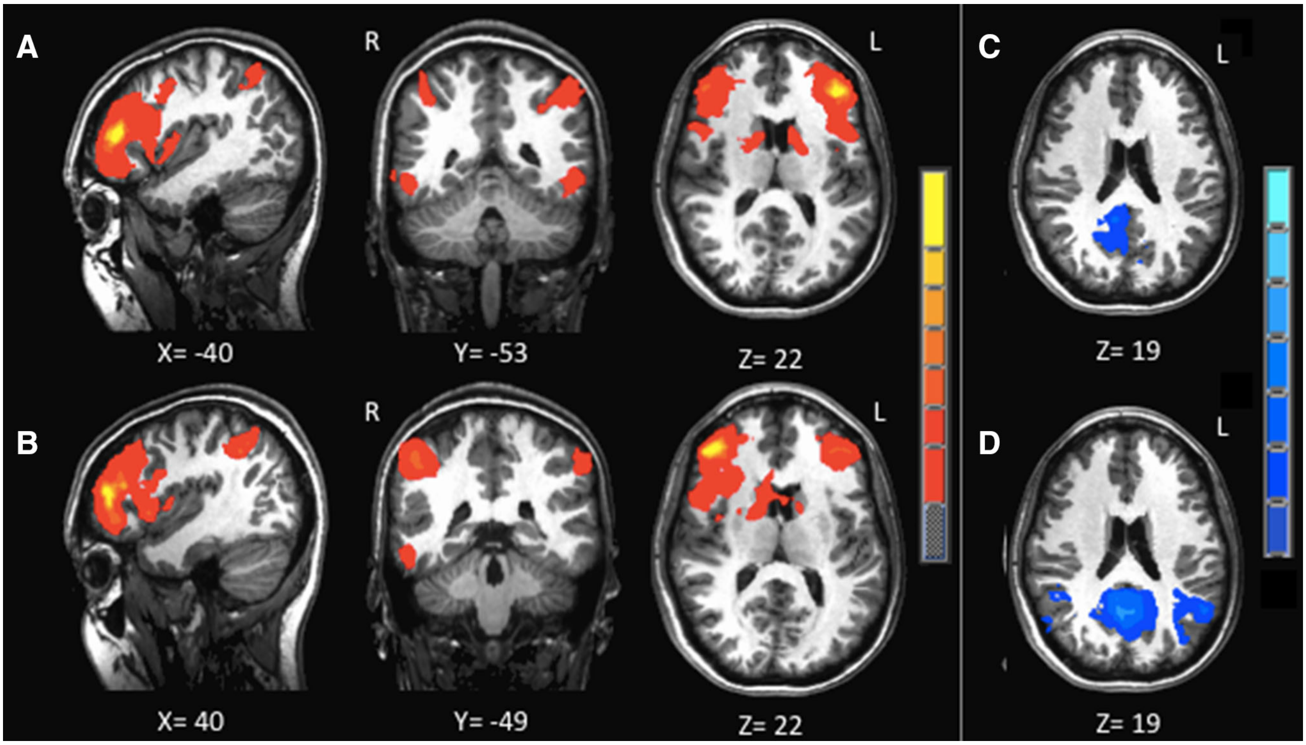

Fig. 2 Functional connectivity of executive network seeds with cortical and subcortical regions. **a** *Left* dlPFC seeds (in *yellow*) positively correlated with activity in the contralateral dlPFC, bilateral caudate, bilateral inferior parietal lobules, and bilateral middle temporal gyrus. **b** *Right* dlPFC seeds (in *yellow*) positively correlated with bilateral inferior parietal lobules and right middle temporal gyrus. Anticorrelations with *left* (panel **c**) and *right* (panel **d**) dlPFC are shown at *right*. Default mode network suppression is indicated by negative correlations of the posterior cingulate cortex, inferior temporal gyrus and angular gyrus regions with dlPFC seeds. Color bars represents *t* values

Crus II, lobule VIIIa and lobule VIIIb (Fig. 4). Connectivity of the cerebellum and dlPFC indicative of cerebellar contribution to executive networks supports recent research proposing non-motor functions of the cerebellum (Krienen and Buckner 2009; Habas et al. 2009; O'Reilly et al. 2010). The right orbital frontoinsula had significantly greater connectivity with bilateral inferior parietal lobules (BA 40) and clusters spanning areas previously demonstrated within the salience network including the contralateral insula, dorsal anterior cingulate cortex, and hypothalamus (Fig. 3a; Seeley et al. 2007; Habas et al. 2009) as well as the left cerebellum Crus I (Fig. 4). The salience network

Table 3 Locations of anticorrelations with executive and salience network seeds

R/L	Brain region (location of maximum intensity)	Max *t* coordinate (*x*, *y*, *z*)	Cluster size (mm^3)	Max *t* value
Left dlPFC seed region				
R	Posterior cingulate cortex (BA 30)	8, −51, 19	98102	−8.372
R	Superior temporal gyrus (BA 38)	56, 11, −16	6800	−5.273
R	Middle temporal gyrus (BA 39)	45, −69, 23	3314	−5.319
L	Cingulate gyrus	−19, −2, 40	2656	−5.386
L	Superior temporal gyrus (BA 22)	−59, 1, 3	2303	−5.019
L	Middle occipital gyrus (BA 19)	−40, −81, −6	1730	−4.481
L	Cerebellum IX	−7, −52,−55	1696	−4.984
R	Cingulate Gyrus	9, −30, 40	1331	−5.669
Right dlPFC seed region				
R	Posterior cingulate cortex (BA 30)	4, −54, 15	220373	−12.158
L	Superior temporal gyrus (BA 22)	−60, −14, −1	10408	−7.147
L	Middle temporal gyrus (BA 39)	−43, −58, 22	7859	−8.075
R	Middle temporal gyrus (BA 39)	52, −69, 13	3056	−5.911
R	Cerebellum IX	7, −48, −55	1513	−8.303
Right orbital frontoinsula seed region				
L	Posterior cingulate cortex (BA 31)	−2, −57, 25	125061	−10.542
L	Superior frontal gyrus (BA 6)	−16, 29, 62	10445	−5.892
R	Precentral gyrus	24, −22, 54	7804	−6.056
L	Inferior parietal lobule (BA40)	−47, −38, 50	3524	−5.093
L	Superior temporal gyrus (BA 38)	−41, 18, −40	2301	−6.021
L	Middle temporal gyrus (BA 21)	−59, −2, −24	2081	−4.982
R	Cerebellum IX	3, −47, −57	2078	−6.514
R	Cingulate gyrus	22, −38, 25	1233	−5.104
L	Cingulate gyrus	−19, −33, 29	1146	−6.478

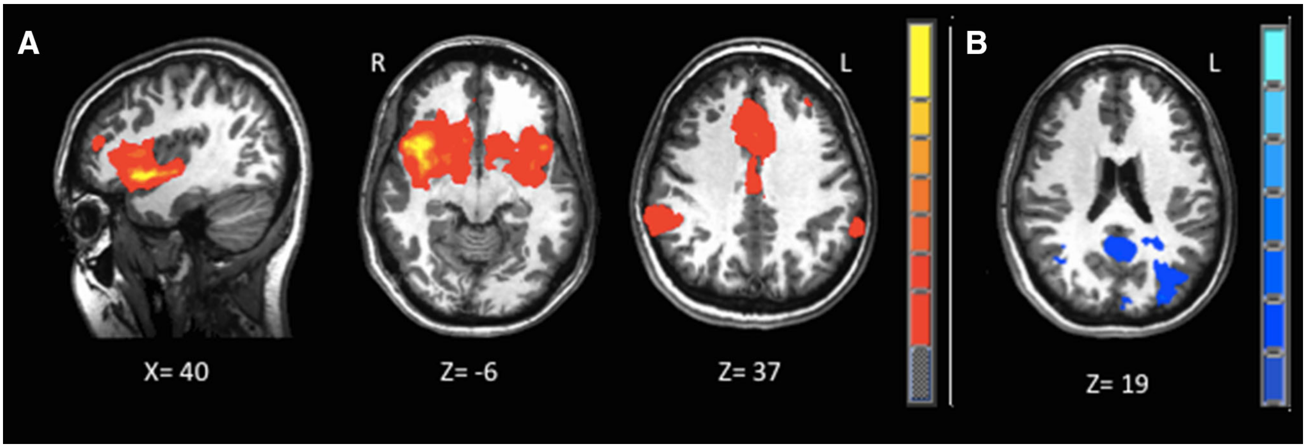

Fig. 3 Cortical and subcortical regions correlating with the right salience network. **a** Seeds placed within the orbital frontoinsula (in *yellow*) positively correlated with activity in the contralateral insula, the cingulate cortex, and bilateral inferior parietal lobules. **b** Orbital frontoinsula seeds negatively correlated with a number of regions, including those within the default mode network such as the posterior cingulate cortex and inferior parietal lobule. *Color bar* represents *t* values

was also anticorrelated with activity in other networks (Table 3). Activity in the orbital frontoinsula seed was negatively correlated with areas attributed to the DMN including the posterior cingulate cortex, superior frontal gyrus, and lateral parietal cortex (Fig. 3b; Watanabe et al. 2012; Zhu et al. 2013).

Between-group analyses

High and Low AMBI groups were compared using an independent samples t-test to ensure significant group differences in self-report scores, $t(24) = -8.922$, $p < 0.001$. A contrast of regions of correlating activity with the dlPFC between the high and low AMBI groups revealed significantly greater connectivity of the high AMBI group between the left dlPFC seed and the dorsal anterior cingulate cortex, which has been linked to attention, emotion and avoidance (Schlund and Cataldo 2010; Spielberg et al. 2011; Yan et al. 2009), see Table 4. For the right dlPFC seed, the high AMBI group demonstrated significantly greater connectivity with the cerebellum Crus I, see Fig. 5. Extracted z values between the right dlPFC and Crus I did not significantly correlate with scores on AMBI, $r_s = 0.177$, $p = 0.388$. Connectivity analyses with seeds at the sensorimotor and salience networks did not find significant differences between these two groups.

Discussion

The cerebellum continues to gain acceptance for its role in cognitive processes. In this study, resting-state fMRI was used to demonstrate intrinsic cerebellar connectivity with non-motor executive connectivity networks and to assess

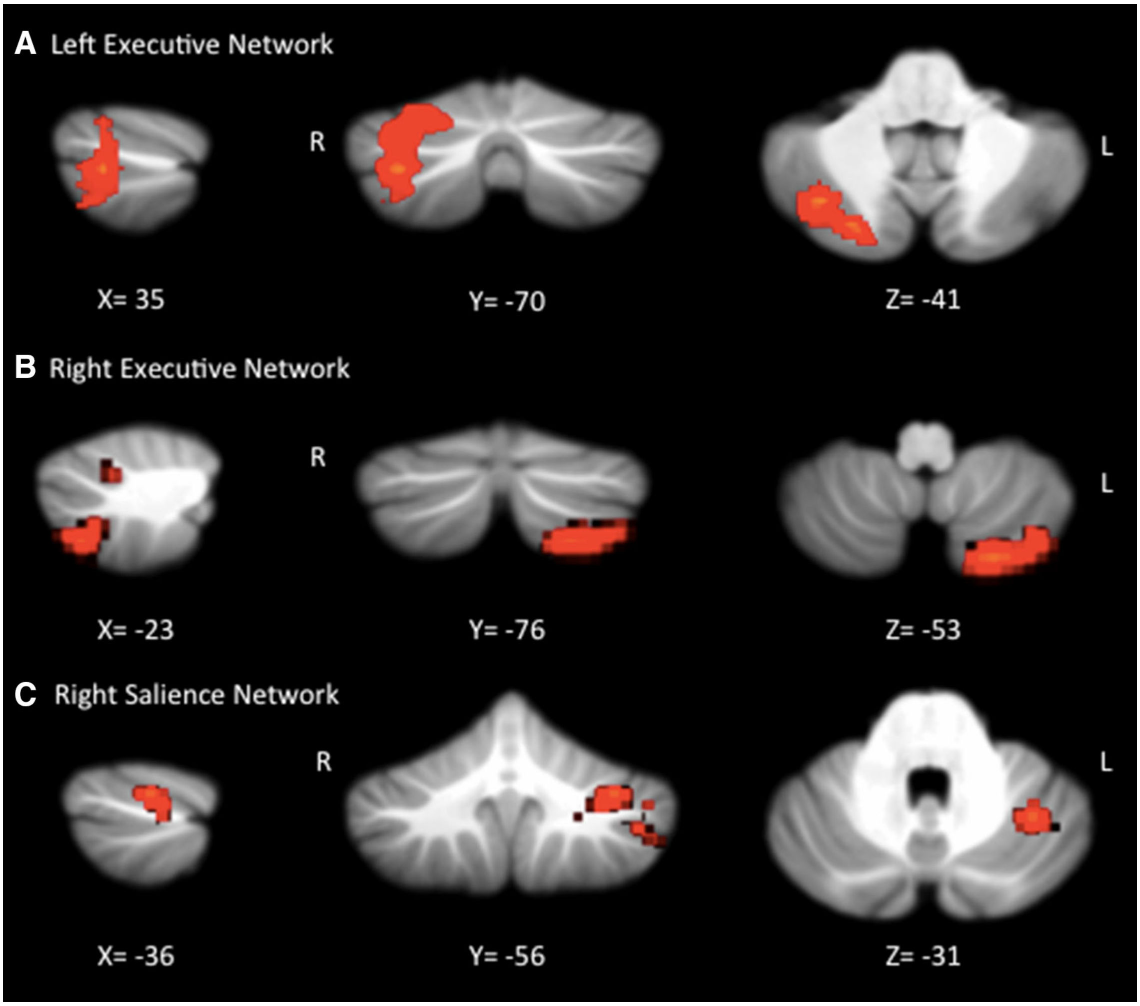

Fig. 4 Cerebellar contributions to executive and salience networks. **a** Significant clusters in the right cerebellum spanning the Crus I, Crus II, and Lobule VIII correlated with activity in the left dlPFC. **b** Similar correlations were observed in the left cerebellum, with significant clusters in lobule VIII correlating with activity in the right dlPFC. **c** Salience network seeds in the right orbital frontoinsula correlated with cerebellar activity in the left cerebellum Crus I

Table 4 Regions of greater connectivity for between-group contrasts of high and low AMBI. BA Brodmann's Area, dlPFC dorsolateral prefrontal cortex

R/L	Brain region	Max *t* coordinate (*x*, *y*, *z*)	Cluster size (mm^3)	Max *t* value
Left dlPFC seed region				
R	Dorsal anterior cingulate cortex	6, 16, 47	1186	3.9803
Right dlPFC seed region				
R	Cerebellum crus I	34, −73, −36	1844	5.0489

BA Brodmann's Area, *dlPFC* dorsolateral prefrontal cortex

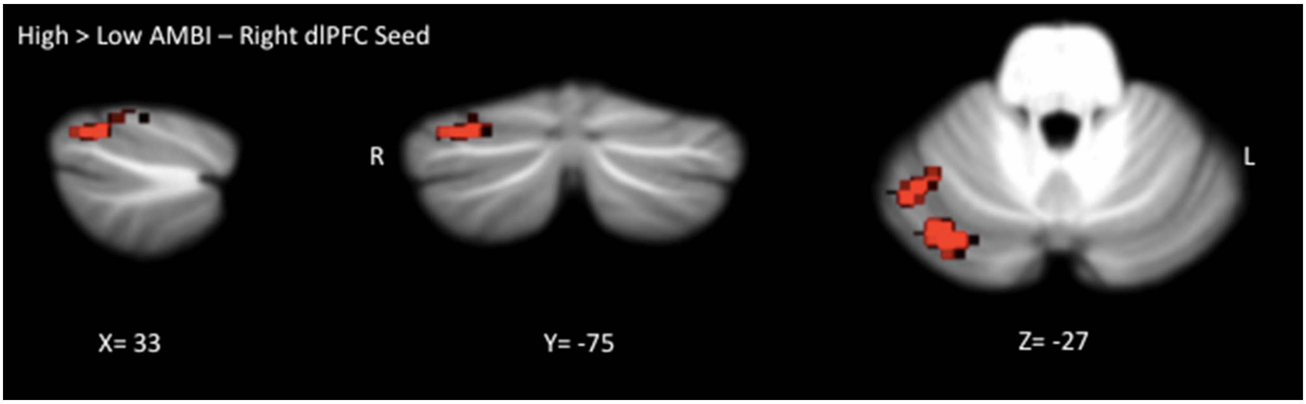

Fig. 5 Group differences in cerebellar connectivity with the executive network. Contrasts indicated significantly greater connectivity for the high AMBI group between the right cerebellum Crus I and the right dlPFC, whole-brain corrected $p < 0.047$, suggesting distinct differences in cerebellar contributions to the executive network in anxiety vulnerability

how connectivity of the cerebellum may differ as a function of anxiety vulnerability. Previous research using retroviral tracing techniques have demonstrated that the Crus I and Crus II of the cerebellum have distinct reciprocal connections to non-motor prefrontal cortical regions (Bostan et al. 2013). These findings support recently published studies establishing connectivity of the Crus I and Crus II with the executive network and other prefrontal cortical regions (Habas et al. 2009; Buckner et al. 2011; Bernard et al. 2012). The present findings provide further support for a cerebellar role in the executive and salience networks.

Overall, we also observed correlations of the intrinsic activity of the cerebellum Crus I and orbital frontoinsula, supporting the conclusion that the cerebellum plays a role in non-motor functioning. The specific correlation of Crus I with the orbital frontoinsula supports distinct contributions previously demonstrated by Habas (2009). For the executive network, it is interesting to note that in the overall group analysis intrinsic activity in motor regions of the cerebellum including lobules V, VIIIa, and VIIIB was correlated with intrinsic activity in the dlPFC. Presently, it is unclear what role(s) lobules V and VIII play in the executive functions of the cerebellum. Clinical studies report strokes in lobule VIII can alter the subjective experience of pleasant feelings (Turner et al. 2007), suggesting it may be involved in emotional processing. A recent meta-analysis reports that cerebellar lobule VIII activated in emotional, language, music and working memory tasks, often co-activating with Crus I and Crus II (E et al. 2014), similar to what we observed with the left dlPFC seed region. As research on the cognitive functions of the cerebellum moves forward more light may be shed on the interplay between motor and executive networks suggested by the relationship between lobules V and VIII and the dorsolateral prefrontal cortex.

An essential component of this study was the between-group comparison between individuals at greater and lesser risk for the development of an anxiety disorder. Previous research in a cerebellar-dependent associative learning task (Caulfield et al. 2013) implies that the cerebellum may play an important role in behavioral inhibition and anxiety vulnerability. We compared behaviorally inhibited (high AMBI) to non-inhibited (low AMBI) participants, using seed regions placed individually for each subject to assess potential differences in functional connectivity between the two groups. Results revealed that intrinsic connectivity between the cerebellum and executive network is influenced by individual differences in anxiety vulnerability as measured by AMBI scores. Between-group differences cannot be attributed to structural differences, as comparisons of segmented and labeled anatomical T1 scans

(Fischl et al. 2002) demonstrated no between-group structural differences, nor could they be attributed to differences in head motion as comparisons of motion in six directions (3 in translation, 3 in rotation) were not significantly different, all p's > 0.360. Furthermore, these differences were not observed between groups in the sensorimotor or salience network. However, behaviorally inhibited individuals show significantly greater connectivity between the right dlPFC and the right cerebellum Crus I. This finding is supported by previous studies demonstrating that extensive portions of the Crus I/Crus II map to prefrontal cortical regions involved in executive control (Habas et al. 2009; O'Reilly et al. 2010; Buckner et al. 2011). Here, we have demonstrated that previously reported connectivity may be driven in part by individual differences.

Research has increased in executive network dysfunction in recent years in areas such as Alzheimer's and schizophrenia (for review see: Rosazza and Minati 2011) but has not assessed anxiety vulnerability. Even more specifically, the role of the cerebellum in anxiety vulnerability has been largely overlooked. The dlPFC, has been shown to be both an essential component of the executive connectivity network (Seeley et al. 2007), and important in processing novelty in the environment and avoidance behaviors (Berns et al. 1997; Aupperle and Paulus 2010; Spielberg et al. 2012)—both of which are representative of the behavioral profile seen in behavioral inhibition. Here, we report that the cerebellum is differentially active in those with behavioral inhibition, suggesting that cerebellar connectivity may play an important role in mediating anxiety. Since this research is at a young stage, it is difficult to determine exactly what role the cerebellum is playing, although multiple possibilities exist. One is that the increased reliance on the cerebellar circuitry may be in response to dysfunction in other systems. For example, hippocampal differences have been related to the development of PTSD (Gilbertson et al. 2006). Furthermore, behaviorally inhibited individuals show enhanced avoidance in a hippocampal dependent avoidance task (Sheynin et al. 2013). It is possible that increased reliance on cerebro-cerebellar circuitry may be the result of hippocampal dysfunction. Another possibility is that cerebro-cerebellar circuitry itself is dysfunctional resulting in individual differences observed in cerebellar-dependent learning tasks (Caulfield et al. 2013, 2015) and in connectivity between the cerebellum and cognitive regions within its circuitry.

Behaviorally inhibited individuals showed significantly greater connectivity between the left dlPFC and right dorsal anterior cingulate (dACC). Increased connectivity between the dACC and dlPFC may play an important role in anxiety vulnerability, especially given the dACC's association with error detection, anticipation, attention, emotional responses, and avoidance—all essential components in anxiety. (Yan et al. 2009; Schlund and Cataldo 2010; Spielberg et al. 2011). Although there were no significant cerebellar differences with the left dlPFC seed, these findings are relevant in terms of the profile of behavior observed in behavioral inhibition, especially in respect to attention, avoidance, and emotion. It must be noted that while cerebellar connectivity in the overall group analysis followed expected contralateral connectivity between the cortex and cerebellum that has been confirmed in recent resting state connectivity studies of the cerebellum (Habas et al. 2009; Buckner et al. 2011), the contrast between high and low AMBI groups revealed a difference in ipsilateral connectivity between groups. In light of anatomical studies indicating that not all cerebro-cerebellar projections are contralateral, with studies in non-human primates indicating that approximately 10 % of projections to the cerebellar hemispheres are ipsilateral (Brodal 1979). Greater ipsilateral connectivity may reflect greater reliance on bilateral cerebellar hemispheres in the high AMBI group, possibly due to individual differences in the distribution of executive network connections to the cerebellum, or perhaps relating to increased demand of modulation of the executive network.

These findings suggest that those with behaviorally inhibited temperament may have greater connectivity between the executive network and areas responsible for attention, avoidance, anticipation and error detection. Such increased connectivity may result in differences in processing of stimuli in the environment. For example, if the regions responsible for vigilance are connected with those responsible for attention, error detection, and avoidance, then the system may misinterpret non-threatening circumstances for situations that call for vigilance. Increased vigilance may lead to internal and external feelings of anxiety and contribute to the cycle of avoidance that is an essential component in the development of anxiety.

Although differences are present in the group level, there was no significant correlation between executive network connectivity and AMBI scores. Previous behavioral studies from our lab have had similar relationships, with close inspection suggesting that less vulnerable individuals have greater variability in their scores, making a correlation between AMBI and other measures difficult. We still feel that the group level differences are important and that future studies with larger samples or targeting only the highest may be useful. Cerebellar involvement in anticorrelations with the executive network also needs to be explored in more detail, as this relationship may highlight the modulatory role of the cerebellum in executive functioning. As this is only the first study of its kind, it is clear that continued research is necessary to fully understand individual differences in functional connectivity and how it relates to anxiety vulnerability. Presently, explanations for anxiety vulnerability concentrate on prefrontal and amygdalar structures, overlooking subcortical regions such as the cerebellum. A full understanding of the relationship between these regions may shed light on the neural substrates underlying anxiety vulnerability.

Acknowledgments The authors would like to thank Scarlett Doyle for scanning support, Elizabeth Wieland for assistance in participant recruitment and data collection, and Dr. Tuuli Morrill for being so accommodating. This work was partially supported by the Stress and Motivated Behavior Institute, the U.S. Department of Veterans Affairs, the Foundations Fellowship of the Graduate School of Biomedical Sciences, and the Departments of Radiology and Psychology at Michigan State University. Scan support was provided by the Michigan State University Radiology Pilot Scan Program.

References

Arnold Anteraper S, Triantafyllou C, Sawyer AT, Hofmann SG, Gabrieli JD, Whitfield-Gabrieli S (2014) Hyper-connectivity of subcortical resting-state networks in social anxiety disorder. Brain Connect 4(2):81–90

Aupperle RL, Paulus MP (2010) Neural systems underlying approach and avoidance in anxiety disorders. Dialogues Clin Neurosci 12:517–531

Beckmann CF, DeLuca M, Devlin JT, Smith SM (2005) Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci 360:1001–1013. doi:10.1098/rstb.2005.1634

Bermpohl F, Pascual-Leone A, Amedi A, Merabet LB, Fregni F, Gaab N, Alsop D, Schlaug G, Northoff G (2006) Dissociable networks for the expectancy and perception of emotional stimuli in the human brain. Neuroimage 30:588–600. doi:10.1016/j.neuroimage.2005.09.040

Bernard JA, Seidler RD, Hassevoort KM, Benson BL, Welsh RC, Wiggins JL, Jaeggi SM, Buschkuehl M, Monk CS, Jonides J, Peltier SJ (2012) Resting state cortico-cerebellar functional connectivity networks: a comparison of anatomical and self-organizing map approaches. Front Neuroanat 6:31. doi:10.3389/fnana.2012.00031

Berns GS, Cohen JD, Mintun MA (1997) Brain Regions Responsive to Novelty in the Absence of Awareness. Science 276:1272–1275

Biederman J, Rosenbaum JF, Hirshfeld DR, Faraone SV, Bolduc EA, Gersten M, Meminger SR, Kagan J, Snidman N, Reznick JS (1990) Psychiatric correlates of behavioral inhibition in young children of parents with and without psychiatric disorders. Arch Gen Psychiatry 47:21–26

Biederman J, Hirshfeld-Becker DR, Rosenbaum JF, Hérot C, Friedman D, Snidman N, Kagan J, Faraone SV (2001) Further evidence of association between behavioral inhibition and social anxiety in children. Am J Psychiatry 158:1673–1679. doi:10.1016/0022-3956(91)90015-3

Biswal B, Yetkin FZ, Haughton VM, Hyde JS (1995) Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 34:537–541

Blackford JU, Avery SN, Shelton RC, Zald DH (2009) Amygdala temporal dynamics: temperamental differences in the timing of amygdala response to familiar and novel faces. BMC Neurosci 10:145. doi:10.1186/1471-2202-10-145

Blackwood N, Ffytche D, Simmons A, Bentall R, Murray R, Howard R (2004) The cerebellum and decision making under uncertainty. Brain Res Cogn Brain Res 20:46–53

Bluhm RL, Williamson PC, Osuch EA, Frewen PA, Stevens TK, Boksman K, Neufeld RWJ, Theberge J, Lanius RA (2009) Alterations in default network connectivity in posttraumatic stress disorder related to early-life trauma. J Psychiatry Neurosci 34:187–194

Bonne O, Gilboa A, Louzoun Y, Brandes D, Yona I, Lester H, Barkai G, Freedman N, Chisin R, Shalev AY (2003) Resting regional cerebral perfusion in recent posttraumatic stress disorder. Biol Psychiatry 54:1077–1086

Bostan AC, Dum RP, Strick PL (2013) Cerebellar networks with the cerebral cortex and basal ganglia. Trends Cogn Sci 17:241–254. doi:10.1016/j.tics.2013.03.003

Brodal P (1979) The pontocerebellar projection in the rhesus monkey: an experimental study with retrograde axonal transport of horseradish peroxidase. Neuroscience 4:193–208

Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BT (2011) The organization of the human cerebellum estimated by intrinsic functional connectivity. J Neurophysiol 106(5):2322–2345

Caulfield MD, McAuley JD, Servatius RJ (2013) Facilitated acquisition of eyeblink conditioning in those vulnerable to anxiety disorders. Front Hum Neurosci. doi:10.3389/fnhum.2013.00348

Caulfield MD, VanMeenen KM, Servatius RJ (2015) Facilitated acquisition of standard but not long delay classical eyeblink conditioning in behaviorally inhibited adolescents. Behav Brain Res 278:476–481

Clauss JA, Avery SN, Blackford JU (2015) The nature of individual differences in inhibited temperament and risk for psychiatric disease: a review and meta-analysis. Prog Neurobiol 127–128:23–45. doi:10.1016/j.pneurobio.2015.03.001

Clower DM, Dum RP, Strick PL (2005) Basal ganglia and cerebellar inputs to 'AIP'. Cereb Cortex 15:913–920

Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP (1976) Chronic cerebellar stimulation in epilepsy clinical and anatomical studies. Arch Neurol 33:559–570. doi:10.1001/archneur.1976.00500080037006

Cordes D, Haughton VM, Arfanakis K, Wendt GJ, Turski PA, Moritz CH, Quigley MA, Meyerand ME (2000) Mapping functionally related regions of brain with functional connectivity MR imaging. AJNR Am J Neuroradiol 21:1636–1644

Cox RW (1996) AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173

Diedrichsen J (2006) A spatially unbiased atlas template of the human cerebellum. Neuroimage 33:127–138

Diedrichsen J, Balsters JH, Flavell J, Cussans E, Ramnani N (2009) A probabilistic atlas of the human cerebellum. Neuroimage 46:39–46

Ding J, Chen H, Qiu C, Liao W, Warwick JM, Duan X, Zhang W, Gong Q (2011) Disrupted functional connectivity in social anxiety disorder: a resting-state fMRI study. Magn Reson Imaging 29:701–711. doi:10.1016/j.mri.2011.02.013

Dum RP, Strick PL (2002) An Unfolded Map of the Cerebellar Dentate Nucleus and its Projections to the Cerebral Cortex. J Neurophysiol 89:634–639. doi:10.1152/jn.00626.2002

E KH, Chen SH, Ho MH, Desmond JE (2014) A meta-analysis of cerebellar contributions to higher cognition from PET and fMRI studies. Hum Brain Mapp 35:593–615. doi:10.1002/hbm.22194

Fischl B, Salat DH, Busa E et al (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355

Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 8:700–711. doi:10.1038/nrn2201

Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van Essen DC, Raichle ME (2005) The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci USA 102:9673–9678. doi:10.1073/pnas.0504136102

Fransson P (2005) Spontaneous low-frequency BOLD signal fluctuations: an fMRI investigation of the resting-state default mode of brain function hypothesis. Hum Brain Mapp 26:15–29. doi:10.1002/hbm.20113

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK (2002) Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat Neurosci 5:1242–1247. doi:10.1038/nn958

Gilbertson MW, Paulus LA, Williston SK, Gurvits TV, Lasko NB, Pitman RK, Orr SP (2006) Neurocognitive function in monozygotic twins discordant for combat exposure: relationship to posttraumatic stress disorder. J Abnorm Psychol 115:484–495. doi:10.1037/0021-843X.115.3.484

Gilboa A, Shalev AY, Laor L, Lester H, Louzoun Y, Chisin R, Bonne O (2004) Functional connectivity of the prefrontal cortex and the amygdala in posttraumatic stress disorder. Biol Psychiatry 55:263–272

Gladstone G, Parker G (2005) Measuring a behaviorally inhibited temperament style: development and initial validation of new self-report measures. Psychiatry Res 135:133–143. doi:10.1016/j.psychres.2005.03.005

Glickstein M, May JG, Mercier BE (1985) Corticopontine projection in the macaque: the distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. J Comp Neurol 235:343–359. doi:10.1002/cne.902350306

Greicius MD, Krasnow B, Reiss AL, Menon V (2003) Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci USA 100:253–258. doi:10.1073/pnas.0135058100

Habas C, Kamdar N, Nguyen D, Prater K, Beckmann CF, Menon V, Greicius MD (2009) Distinct cerebellar contributions to intrinsic connectivity networks. J Neurosci 29:8586–8594. doi:10.1523/JNEUROSCI.1868-09.2009

Habel U, Klein M, Kellermann T, Shah NJ, Schneider F (2005) Same or different? Neural correlates of happy and sad mood in healthy males. Neuroimage 26:206–214. doi:10.1016/j.neuroimage.2005.01.014

Hahn A, Stein P, Windischberger C, Weissenbacher A, Spindelegger C, Moser E, Kasper S, Lanzenberger R (2011) Reduced resting-state functional connectivity between amygdala and orbitofrontal cortex in social anxiety disorder. Neuroimage 56:881–889. doi:10.1016/j.neuroimage.2011.02.064

Heath RG, Cox AW, Lustick LS (1974) Brain activity during emotional states. Am J Psychiatry 131:858–862. doi:10.1176/appi.ajp.131.8.858

Hirshfeld D, Rosenbaum J, Biederman J (1992) Stable behavioral inhibition and its association with anxiety disorder. J Am Acad Child Adolesc Psychiatry 31:103–111

Hofer A, Siedentopf CM, Ischebeck A, Rettenbacher MA, Verius M, Felber S, Wolfgang Fleischhacker W (2007) Sex differences in brain activation patterns during processing of positively and negatively valenced emotional words. Psychol Med 37:109–119. doi:10.1017/S0033291706008919

Holloway JL, Allen MT, Myers CE, Servatius RJ (2013) Behaviorally inhibited individuals demonstrate significantly enhanced conditioned response acquisition under non-optimal learning conditions. Behav Brain Res 261C:49–55. doi:10.1016/j.bbr.2013.10.041

Jang JH, Kim J-H, Jung WH, Choi J-S, Jung MH, Lee J-M, Choi C-H, Kang D-H, Kwon JS (2010) Functional connectivity in fronto-subcortical circuitry during the resting state in obsessive-compulsive disorder. Neurosci Lett 474:158–162. doi:10.1016/j.neulet.2010.03.031

Kelly RM, Strick PL (2003) Cerebellar loops with motor cortex and prefrontal cortex of a nonhuman primate. J Neurosci 23:8432–8444

Kiviniemi V, Kantola J-H, Jauhiainen J, Hyvärinen A, Tervonen O (2003) Independent component analysis of nondeterministic fMRI signal sources. Neuroimage 19:253–260

Knyazev GG (2007) Motivation, emotion, and their inhibitory control mirrored in brain oscillations. Neurosci Biobehav Rev 31:377–395. doi:10.1016/j.neubiorev.2006.10.004

Krienen FM, Buckner RL (2009) Segregated fontro-cerebellar circuits revealed by intrinsic functional connectivity. Cereb Cortex 19:2485–2497

Lanius RA, Bluhm RL, Coupland NJ, Hegadoren KM, Rowe B, Theberge J, Neufeld RWJ, Williamson PC, Brimson M (2010) Default mode network connectivity as a predictor of post-traumatic stress disorder symptom severity in acutely traumatized subjects. Acta Psychiatr Scand 121:33–40. doi:10.1111/j.1600-0447.2009.01391.x

Lee GP, Meador KJ, Loring DW, Allison JD, Brown WS, Paul LK, Pillai JJ, Lavin TB (2004) Neural substrates of emotion as revealed by functional magnetic resonance imaging. Cogn Behav Neurol 17:9–17

Liao W, Chen H, Feng Y, Mantini D, Gentili C, Pan Z, Ding J, Duan X, Qiu C, Lui S, Gong Q, Zhang W (2010a) Selective aberrant functional connectivity of resting state networks in social anxiety disorder. Neuroimage 52:1549–1558. doi:10.1016/j.neuroimage.2010.05.010

Liao W, Qiu C, Gentili C, Walter M, Pan Z, Ding J, Zhang W, Gong Q, Chen H (2010b) Altered effective connectivity network of the amygdala in social anxiety disorder: a resting-state FMRI study. PLoS One 5:e15238. doi:10.1371/journal.pone.0015238

Liddle PF, Kiehl KA, Smith AM (2001) Event-related fMRI study of response inhibition. Hum Brain Mapp 12:100–109

Middleton FA, Strick PL (2001) Cerebellar projections to the prefrontal cortex of the primate. J Neurosci 21:700–712

Mineka S, Zinbarg R (2006) A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. Am Psychol 61:10–26. doi:10.1037/0003-066X.61.1.10

Nashold BSJ, Slaughter DG (1969) Effects of stimulating or destroying the deep cerebellar regions in man. J Neurosurg 31:172–186. doi:10.3171/jns.1969.31.2.0172

O'Reilly JX, Beckmann CF, Tomassini V, Ramnani N, Johansen-Berg H (2010) Distinct and overlapping functional zones in the cerebellum defined by resting state functional connectivity. Cereb Cortex 20:953–965. doi:10.1093/cercor/bhp157

Putman P (2011) Resting state EEG delta-beta coherence in relation to anxiety, behavioral inhibition, and selective attentional processing of threatening stimuli. Int J Psychophysiol 80:63–68. doi:10.1016/j.ijpsycho.2011.01.011

Rabinak CA, Angstadt M, Welsh RC, Kenndy AE, Lyubkin M, Martis B, Phan KL (2011) Altered amygdala resting-state functional connectivity in post-traumatic stress disorder. Front Psychiatry 2:62. doi:10.3389/fpsyt.2011.00062

Rorden C, Karnath H-O, Bonhilha L (2007) Improving lesion-symptom mapping. J Cogn Neurosci 19:1081–1088

Rosazza C, Minati L (2011) Resting-state brain networks: literature review and clinical applications. Neurol Sci 32:773–785. doi:10.1007/s10072-011-0636-y

Schall U, Johnston P, Lagopoulos J, Jüptner M, Jentzen W, Thienel R, Dittmann-Balçar A, Bender S, Ward PB (2003) Functional brain maps of Tower of London performance: a positron emission tomography and functional magnetic resonance imaging study. Neuroimage 20:1154–1161

Schlund MW, Cataldo MF (2010) Amygdala involvement in human avoidance, escape and approach behavior. Neuroimage 53:769–776. doi:10.1016/j.neuroimage.2010.06.058

Schmahmann JD (1991) An emerging concept: the cerebellar contribution to higher function. Arch Neurol 48:1178–1187

Schmahmann JD, Pandya DN (1997) Anatomic organization of the basilar pontine projections from prefrontal cortices in rhesus monkey. J Neurosci 17(1):438–458

Schmahmann JD, Macmore J, Vangel M (2009) Cerebellar stroke without motor deficit: clinical evidence for motor and non-motor domains within the human cerebellum. Neuroscience 162:852–861. doi:10.1016/j.neuroscience.2009.06.023

Schwartz CE, Snidman N, Kagan J (2012) Adolescent social anxiety as an outcome of inhibited temperament in childhood. J Am Acad Child Adolesc Psychiatry 38:1008–1015

Seeley WW, Menon V, Schatzberg AF, Keller J, Glover GH, Kenna H, Reiss AL, Greicius MD (2007) Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci 27:2349–2356

Sheynin J, Shikari S, Gluck MA, Moustafa AA, Servatius RJ, Myers CE (2013) Enhanced avoidance learning in behaviorally inhibited young men and women. Stress 16:289–299. doi:10.3109/10253890.2012.744391

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage 23(Suppl 1):S208–S219

Spielberg JM, Miller GA, Engels AS, Herrington JD, Sutton BP, Banich MT, Heller W (2011) Trait approach and avoidance motivation: lateralized neural activity associated with executive function. Neuroimage 54:661–670. doi:10.1016/j.neuroimage.2010.08.037

Spielberg JM, Miller GA, Warren SL (2012) A brain network instantiating approach and avoidance motivation. Psychophysiology 49:1200–1214

Spielberger CD, Gorsuch R, Lushene R, Vagg PR, Jacobs GA (1983) Manual for the State-Trait Anxiety Inventory (Form Y). Consulting Psychologists Press, Palo Alto

Sripada RK, King AP, Garfinkel SN, Wang X, Sripada CS, Welsh RC, Liberzon I (2012) Altered resting-state amygdala functional connectivity in men with posttraumatic stress disorder. J Psychiatry Neurosci 37:241–249. doi:10.1503/jpn.110069

Turner BM, Paradiso S, Marvel CL, Pierson R, Boles Ponto LL, Hichwa RD, Robinson RG (2007) The cerebellum and emotional experience. Neuropsychologia 45:1331–1341. doi:10.1016/j.neuropsychologia.2006.09.023

Van Overwalle F, Baetens K, Marien P, Vandekerckhove M (2014) Social Cognition and the cerebellum: a meta-analysis of over 350 fMRI studies. Neuroimage 86:554–572

Ward B (2000a) Deconvolution analysis of fMRI time series Data, Milwaukee

Ward B (2000b) Simultaneous inference for fMRI data, Milwaukee

Watanabe T, Hirose S, Wada H, Imai Y, Machida T, Shirouzu I, Konish S, Miyashita Y, Masuda N (2012) A pairwise maximum entropy model accurate describes resting-state human brain networks. Nature Communications 4:1370

Xiong J, Parsons LM, Gao JH, Fox PT (1999) Interregional connectivity to primary motor cortex revealed using MRI resting state images. Hum Brain Mapp 8:151–156

Yan H, Zuo X-N, Wang D, Wang J, Zhu C, Milham MP, Zhang D, Zang Y (2009) Hemispheric asymmetry in cognitive division of anterior cingulate cortex: a resting-state functional connectivity study. Neuroimage 47:1579–1589. doi:10.1016/j.neuroimage.2009.05.080

Zhu DC, Majumdar S, Korolev IO, Berger KL, Bozoki AC (2013) Alzheimer's disease and amnestic mild cognitive impairment weaken connections within the default-mode network: a multimodal imaging study. J Alzheimers Dis 34(4):969–984