The role of cerebellum in unipolar and bipolar depression: a review of the main neurobiological findings

Il ruolo del cervelletto nella depressione unipolare e bipolare: una rassegna delle principali evidenze neurobiologiche

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SUMMARY. Evidences from studies on patients with overt cerebellar diseases as well as on healthy individuals suggest a possible role for the cerebellum in cognition, mood and behaviour. The aim of the present study is to review those neuroimaging studies examining the cerebellum in Bipolar Disorder (BD) and Major Depressive Disorder (MDD) and to illustrate a possible role of cerebellum in their pathophysiological mechanisms. Cellular and molecular findings from *post mortem* studies such as mitochondria abnormalities, brain-derived neurotrophic factor and its high affinity receptor tyrosine kinase B, transcription factor specificity protein 4, the glial fibrillary acidic protein have also been reviewed. In total 28 studies have been included in the review; among these, 12 studies were related to structural and functional neuroimaging of cerebellum in BD, 13 studies to structural and functional neuroimaging in MDD and 4 studies to cellular and molecular issues. This wealth of evidence from contemporary studies, indicating that the cerebellum (vermis in particular) is engaged in the modulation of emotional processing, provides strong support for the clinical relevance of cerebellar-limbic connections, and is in agreement with earlier clinical and electrophysiological studies that lead to the indication of the cerebellum as an "emotional pacemaker".

KEY WORDS: cerebellum, unipolar depression, bipolar depression, neuroimaging.

RIASSUNTO. Evidenze derivanti da numerosi studi condotti sia su pazienti affetti da patologie cerebellari sia su soggetti sani suggeriscono che il cervelletto eserciti, oltre a un ruolo ormai ben definito nel controllo e nella regolazione delle funzioni motorie, una significativa attività di modulatore del tono dell'umore, del comportamento e delle funzioni cognitive. In questo lavoro di revisione abbiamo passato in rassegna tutti quegli studi di neuroimaging volti a indagare la presenza di alterazioni cerebellari sia morfologiche sia funzionali in pazienti affetti da disturbo bipolare (DB) e disturbo depressivo maggiore (DDM), ipotizzando l'esistenza di un meccanismo fisiopatologico alla base di questi disturbi, che coinvolga, almeno in parte, il cervelletto. Allo stesso scopo, sono stati esaminati anche quegli studi *post mortem* che indagavano la presenza di alterazioni cellulari e molecolari a partire da campioni di tessuto cerebellare, per esempio alterazioni delle proteine mitocondriali, della tirosinchinasi B e del brain-derived neurotrophic factor (BDNF), del fattore di trascrizione SP4, della proteina fibrillare acida della glia (GFAP). In totale sono stati esaminati 28 studi, 12 inerenti le alterazioni morfologiche e funzionali del cervelletto nel DB, 13 inerenti le alterazioni morfologiche e funzionali del cervelletto nel DDM e 4 inerenti le alterazioni cerebellari *post mortem* in entrambi i disturbi. Dal nostro lavoro di revisione, in linea con quanto presente nella letteratura internazionale, emerge l'interessante ipotesi che il cervelletto funzioni come un "pacemaker emotivo" e che quindi una sua lesione potrebbe tradursi nell'incapacità dell'individuo di rimanere in equilibrio sulla sottile linea dell'eutimia, giustificando in questo modo la comparsa di profonde oscillazioni emotive sia sul versante depressivo sia su quello maniacale.

PAROLE CHIAVE: cervelletto, depressione unipolare, depressione bipolare, neuroimaging.

INTRODUCTION

The role of the cerebellum has traditionally been limited to coordination of voluntary movement, gait, posture, speech and motor function. However, evidences from studies of patients with overt cerebellar diseases as well as from normal subjects, suggest a possible role for the cerebellum in cognition, mood and behaviour[1,2].

The proposal that the cerebellum is involved in the experience and regulation of mood and emotions was posited more than half a century ago[3], and the discovery of intimate afferent and efferent connections to the brainstem and limbic system have provided a neuroanatomical substrate to this theory[4]; cerebellum has monosynaptic projections not only to the hypothalamus, septum, hippocampus, amygdale, and basal ganglia, but also to the brainstem nuclei, where the

cerebellar projections stimulate dopamine and noradrenaline release by innervating the substantia nigra and locus coeruleus[5-7].

One of the first reports to relate the cerebellum to emotional experience involved a patient who reported unpleasant feelings after electrical stimulation of the dentate nucleus and superior peduncle[8]. Furthermore, electrophysiological responses in several limbic structures, including the hippocampus, amygdala, and septum, were recorded following electrical stimulation of the fastigial portion of the deep cerebellar nuclei in mammals[4]. Additional support for the involvement of cerebellum in emotional processes in humans is provided by reports of an emotionally disturbed patient who received electrical stimulation in the fastigial nucleus[4]. It was found that electrical discharges induced by electric stimulation correlated with the patient's experience of anger and tension. Moreover, cerebellar electrode implantation and subsequent chronic cerebellar stimulation for neurologic disorders can yield decreased anxiety and improved mood[9] and has also been reported helpful in some patients with psychiatric (especially depressive) disorders[10].

In line with the suggested role of the cerebellum in mood and behaviour is the abundance of serotonergic and noradrenergic inputs to the cerebellum, and their ability to modulate the cerebellar circuitry and to affect cerebellar learning and control mechanisms[11]. Stoodley and Schmahmann[12] hypothesized the existence of a functional cerebellar dichotomy such that the anterior lobe (lobules I-V) and lobule VIII are predominantly sensorimotor, whereas lobules VI and VII (including Crus I and II and lobule VIIB) contribute to higher-level processes such as cognition and mood regulation. Recent clinical findings provide support for regional functional specialization in cerebellum of cognitive and affective processes, and they point to the posterior lobe, not the anterior lobe, as being critical in this regard[13-15].

Hence, a "cerebellar cognitive affective syndrome" (CCAS) due to disrupted cerebellar modulation of cerebello-parieto-temporo-limbic-prefrontal circuits has been proposed[16]. This syndrome is characterized by a range of executive, visual-spatial, linguistic, behavioural and affective deficits in patients with cerebellar damage. The recognition of the CCAS established the clinically relevant parameters of the nonmotor aspects of cerebellar function. It was apparent from the outset that the CCAS occurs following lesions of cerebellar posterior lobe but not the anterior lobe. The dysregulation of affect noted in the CCAS included hypometric symptoms such as passivity, blunting of affect, and withdrawal on one hand, and hypermetric emotional lability, disinhibition and inappropriate behavior on the other; these could cycle rapidly in the same person, or indeed coexist simultaneously[16].

In contradistinction to the relevant body of neuroimaging and *post mortem* studies examining cerebellar functioning in schizophrenia (SCZ), there are very few studies examining cerebellum in mood disorder. However, in the past 20 years, neuroimaging techniques, such as magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance spectroscopy (MRS) and functional MRI (fMRI), have produced a proliferation of studies that attempted to clarify the neural substrates of bipolar disorder (BD) and major depressive disorder (MDD).

Given the above, the aim of the present paper is to review all those *post mortem* and neuroimaging studies examining the cerebellum in BD and MDD and to illustrate a possible role of cerebellum in their pathophysiological mechanisms.

BIPOLAR DISORDER

BD is a common, life-long progressive illness that typically begins in adolescence, with a lifetime prevalence of about 3% in the general population[17-20]. Despite being a common and important psychiatric illness, the specific neurobiological basis of BD is still not clear. The disorder is characterized by a wide range of symptoms, such as affective instability, neurovegetative abnormalities, sleep disorders, impulsivity and psychotic features, that suggest a dysfunction in anterior limbic networks that subsume these behavioral functions[17,18,21-23]. Neuroanatomic studies have therefore focused on components of these networks that include prefrontal-striatal-thalamic circuits and closely connect areas such as the amygdale and midline cerebellum[24].

Structural neuroimaging studies

Early computerized tomography studies revealed smaller total cerebellar size in adult BD patients compared to SCZ patients and healthy controls[25], and a relationship between vermal volume abnormalities and repeated BD illness episodes have been also reported.

Del Bello et al.[26] measured the size of the cerebellar vermis in BD patients with multiple prior affective episodes, in first-episode patients and in healthy subjects. In this study, the multiple-episode patients exhibited decreased vermal size (cerebellar region V3, lobules VIII-X) compared with first episode patients and healthy subjects; this finding was confirmed by Brambilla et al. in 2001[27], who showed a trend for an inverse correlation between number of episodes and vermis area V3. Mills et al.[28] have recently replicated this data and extended them to include vermal area II. These vermal regions project to the orbitomesial cortex, anterior cingulate gyrus, amygdala, hippocampal and dentate gyri, and pyriform and periamygdaloid cortical regions, as well as the hypothalamus, all of which are believed to regulate mood. They did not find significant relationships among vermal subregional volumes and prior number of episodes of mania or depression. However, they found an association between V3 volume and antidepressant exposure, suggesting their previous finding may have been an artifact of treatment for depression.

In a recent MRI study, Monkul et al.[29] examined anatomical abnormalities in the cerebellum and vermis in young BD patients and healthy subjects. They did not find statistically significant differences between BD patients early in their illness course and age matched healthy controls in any of the measured regions; however, there was also a significant inverse correlation between the number of prior affective episodes and V2 area in male bipolar subjects.

Functional neuroimaging studies

There is a small number of functional neuroimaging studies addressing BD, and those examining the cerebellum are even less common.

In a study conducted by Ketter et al. in 2001[30], 43 medication-free, treatment-resistant, predominantly rapid-cycling BD patients and 43 healthy control subjects had cerebral glucose metabolism assessed using PET. The patient sample was subdivided using three clinical parameters: mood state (depressed, mildly depressed, euthymic), bipolar subtype (bipolar I, bipolar II) and rapid-cycling status (currently rapid cycling, non-rapid cycling). Increased cerebello-posterior cortical metabolism was seen in all patient subgroups compared to control subjects, independently from mood state, disorder subtype, or cycle frequency. The cerebello-posterior cortical hypermetabolism seen in all bipolar subgroups (including euthymic) suggested a possible congenital or acquired trait abnormality.

Other functional neuroimaging studies have noted abnormalities in the cerebellum among euthymic adults with BD[31-32]. Decreased activation in the cerebellum has been observed in response to positive affect induction and during a counting Stroop interference task[32,33].

One study compared patients with SCZ to those with BD and healthy controls; both schizophrenic and BD patients were on conventional antipsychotic medication[34]. In this study, patients with BD had the lowest measures of cerebellar blood volume, whereas the schizophrenic patients had the highest measures.

Benson et al.[35] explored the patterns of cerebral metabolic functional associativity in patients with both MDD and BD in comparison to healthy controls: associativity was defined as the correlative metabolic relationships between brain regions[36]. In BD patients, the associative relationships of the cerebellar hemispheres with the rest of the brain displayed a loss of inverse correlations with prefrontal areas as well as with the right anterior and posterior temporal cortex. Specifically, in patients with BD both cerebellar lobes lacked significant negative correlations with the superior, medial and midfrontal cortex bilaterally. In MDD patients, the general correlative pattern of bilateral cerebellar metabolism appeared closer to that observed in healthy controls than that observed in BD patients, though to a diminished spatial extent. In contrast to the BD patients and the controls, MDD patients also showed negative correlations between both cerebellar hemispheres and the region including the left extended amygdala, ventral striatum and insula; these relationships were significantly more negative than in controls. Moreover, the normal patterns of inverse associations between the dorsolateral prefrontal cortex (DLPFC) and more posterior cortical and subcortical areas, such as the cerebellum and amygdala, were virtually absent in both BD and MDD patients. This could be a reflection of the previous findings of relative cerebellar hyperactivity in BD[30] and MDD[37], as well as of an absolute prefrontal hypometabolism in BD and MDD patients[37,38].

Cellular and molecular findings

Although several molecular alterations have been identified in the prefrontal cortex of BD patients, little is known about the molecular changes that occur in the cerebellum[39,40].

Transcription factor specificity protein 4 (SP4) and the closely related factor SP1, have recently been reported to be involved in psychiatric diseases. Recent findings point to an association of SP4 gene to psychiatric diseases including BD[41,42], while altered SP1 expression has been reported in patients with schizophrenia[43]. SP4 is broadly expressed in neurons of the central nervous system with higher levels in the cerebellum and hippocampus[44,45], while Sp1 is expressed ubiquitously in the organism. SP4 and SP1 regulate expression of genes implicated in a variety of biological processes including neuronal development and function[46,47]. Pinacho et al.[48] reported that protein, but not mRNA, levels of SP4 are reduced in the *post mortem* cerebellum of BD patients. Interestingly, some microarray studies[49,50] raise the possibility that lithium controls SP4 through altered expression of components in the ubiquitin/proteasome pathway such as proteasome subunit beta type 5 (PSMB5). Interestingly, Pinacho et al.[48] found that SP4 mRNA levels were reduced upon lithium treatment. The observation that lithium also increased SP1 protein levels in cerebellar granule neurons under conditions of membrane depolarization suggests that lithium treatment could counteract the decrease observed for both factors in cerebellum of BD subjects and thus both these SP factors may be susceptible to be targeted by new therapeutic approaches to BD.

Genetic studies also implicate mitochondria abnormalities in SCZ and in affective disorders. For example, two single nucleotide polymorphisms (SNPs) in a nuclear encoded subunit of complex I, NDUFV2, were found to be associated with SCZ and with BD[51,52]. Genetic variations in mitochondrial DNA encoded ND3 and ND4 subunits of complex I were associated with BD and schizophrenia, respectively[53,54]. These studies suggest the genetic variation in complex I as a risk factor in both disorders. In BD a reduction in the expression level of mitochondrial genes, including those of the mitochondrial oxidative phosphorylation system (OXPHOS) was observed in hippocampal and prefrontal *post mortem* specimens[55,56], while an increase in complex I subunits NDUFV1 and NDUFV2 was observed in the parieto-occipital cortex[57].

Ben-Shachar and Karry[58] compared mRNA and protein levels of three subunits of mitochondrial complex I (NDUFV1, NDUFV2 and NDUFS1) in different brain areas of schizophrenic, bipolar and depressed patients and normal subjects. The main finding of the this study was that complex I subunits were altered in all three psychiatric disorders, albeit in a disease specific neuroanatomical pattern. In both affective disorders, reductions in complex I subunits were observed specifically in the cerebellum, with the depressed group demonstrating more consistent alterations. The results of this study indicate that the lateral hemisphere of the cerebellum seems to be a prominent anatomical substrate for depression; in fact, the most consistent alterations were observed both in MDD and BD patients (as expected by the overlap of symptoms).

Tyrosin kinase B, cerebellum and bipolar disorder

Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and BDNF high affinity receptor tyrosine ki-

nase B (TrkB) are widely expressed in the central nervous system (CNS) and play a crucial role in regulating synaptic transmission and plasticity during development and adulthood[59-66].

In addition to full-length TrkB (TrkB-FL) with an intact tyrosine kinase domain, alternative splicing of the TrkB pre-mRNA generates C-terminus-truncated isoforms lacking tyrosine kinase, such as T1 and T-Shc isoforms found in the human brain[67]. In the adult primate cerebellum, BDNF and TrkB are expressed in almost all Purkinje and granule cells[71]. Specifically in the developing cerebellum, BDNF-induced TrkB-FL signaling is implicated in the formation of climbing fiber-Purkinje cell synapses, and the switch from full-length to truncated TrkB expression in inferior olivary neurons is associated with elimination of climbing-fiber multi-innervation to leave mature Purkinje cells mono-innervated[72].

Soontornniyomkij et al.[70] studied protein expression levels of BDNF and TrkB in the cerebellar inferior semilunar lobule of patients with schizophrenia, BD, and MDD in comparison to those levels found in unaffected control subjects, finding a decreased TrkB protein expression in the BD group. The truncated isoform TrkB-T1 appeared to represent the majority of TrkB protein expressed in this specific cerebellar region. This study suggested that the alteration in TrkB protein expression in BD is attributable to the disease process, as they found no significant difference in TrkB protein expression between the psychotic and non-psychotic groups. It has been proposed that TrkB-T1 may function as a dominant negative receptor to sequester BDNF and inhibit its downstream effects, such as autophosphorylation of TrkB-FL, Ca2+ efflux, neurite outgrowth, and cell survival activity[61]. Based on this proposed mechanism, the reduction of TrkB-T1 protein expression in the cerebellar cortex observed in Soontornniyomkij et al. study may represent, as the authors suggest, a compensatory response to deficiencies in synaptic plasticity mediated by other mechanisms in BD[71,72].

Given the role of TrkB signaling in synaptic plasticity, decreased TrkB expression in the cerebellum of patients with BD suggests that dysregulation of neurotrophin-induced TrkB activation in the cerebellum may play a role in the pathophysiology of BD.

MAJOR DEPRESSIVE DISORDER

In recent decades there has been a significant increase in the number of researches that have drawn attention to MDD[73-76] and a possible role of the cerebellum in the phatophysiology of MDD emerged[77].

Structural neuroimaging studies

There are very few studies examining cerebellar size in MDD. Early MRI studies[78,79] showed reduced cerebellar size in patients with MDD, whereas a quantitative MRI investigation failed to find any statistically significant differences[80].

Recently, Lee et al.[81] demonstrated a significantly decreased gray matter density (GMD) among depressed patients in the thalamus, nucleus accumbens, fusiform gyrus, lingual gyrus, and the central lobule of the cerebellum. Peng et al.[82] examined the structural difference in regional GMD between 22 first-episode MDD patients and 30 healthy controls by optimized VBM based on MRI. Their VBM findings revealed a smaller gray matter for the left cerebellum, suggesting that the left cerebellar hemisphere may be involved in the pathophysiology of MDD. The findings of simultaneous gray matter reduction in the left cerebellum and the right dorsolateral prefrontal cortex (DLPFC) led the authors to propose that prefronto-cerebellar circuit structural abnormalities may sub serve the emotional and cognitive function deficits encountered in MDD.

Sassi and Soares[83] found that cerebellar atrophy is related to severity and non response to antidepressant treatment. In the same study, cognitive deficits in depressed patients were related to lower cerebellar cortex activity in PET analyses. Neuroanatomical studies have shown that cerebellar hemispheres project to the contralateral DLPFC through dentothalamic fiber tracts. Cortical regions that receive cerebellar output project back to the cerebellum, thus forming closed prefronto-cerebellar circuit[84]. These connections are assumed to be of critical importance to the alleged involvement of the cerebellum in emotional and cognitive functions[35].

Functional neuroimaging studies

Dolan et al.[85] were the first to report an increase in baseline cerebellar vermal blood flow in a subset of patients with depression and cognitive impairment. The authors also found a negative correlation between total cerebellar tissue volume and baseline depression scores. A meta-analytic study showed reduced posterior cerebellar hemisphere activation to positive emotion in depressed group compared with healthy controls[86]. An fMRI study showed reduced activation in lateral cerebellum during anticipation of the noxious stimulus in women who had recovered from MDD, suggesting that depression may impart a permanent and irreversible change in cerebellar function[87]. Liu et al.[88] found that depressed patients and their first-degree relatives exhibited a significantly decreased regional homogeneity (ReHo) in the right insula and left cerebellum compared with controls. Their results are in accord with the above findings in indicating the involvement of cerebellar dysfunction in MDD.

One SPECT study showed that MDD patients with psychotic features had significantly lower rCBF perfusion ratios in left parietal cortex and in left cerebellum than MDD patients without psychotic features[89]. As both groups had similar psychometric scores, these differences could not be explained by the severity of depressive symptoms and might be related to poorer cognitive performance. These patients showed similar dysfunctional areas as in the model of "Cognitive Dysmetria". Thus, one may speculate that cognitive dysmetria model can be valid for psychotic symptom formation in major depression. However, we should be very cautious about establishing an association between SCZ and psychotic depression, since different pathophysiological mechanisms might influence the circuits responsible for generating the negative and psychotic symptoms in SCZ and depression[90] and the findings should be confirmed in further studies using advanced neuroimaging methods.

In a study conducted by Dichter et al.[91], a monetary incentive delay task was used during fMRI scanning to assess neural responses in frontostriatal reward regions during reward anticipation and outcomes in 19 participants with remitted MDD (rMDD) and in 19 matched control participants. During the anticipation phase of the task, the rMDD group was characterized by relatively greater activation in the right cerebellum, in bilateral anterior cingulate gyrus and right midfrontal gyrus. The finding of increased activation in right cerebellum in rMDD requires replication; however it may be linked to the extensive projections from this region to different areas of the reward network[92].

THE EFFECT OF MEDICATIONS ON NEUROIMAGING OF CEREBELLUM

Loeber et al.[93] investigated whether differential drug effects would be observed on cerebellar blood volume in a cohort of bipolar patients. Patients on conventional antipsychotics had the lowest mean absolute blood volume measures for all cerebellar regions, whereas those on atypical antipsychotics had the highest blood volume measures. Comparison subjects had cerebellar blood volume measures in the middle, with results closer to subjects in the atypical group. This study found a strong association between cerebellar blood volume in patients with BD and type of antipsychotic medication. In contrast, lithium seemed to have little or no effect on cerebellar blood volume in the current study group. This finding has important implications for experiments aimed at measuring levels of functional activity; in particular it may be important in those studies that are dependent on cerebral vasculature in patients treated with antipsychotic medications[94].

CEREBELLUM, GLIAL CELL AND MOOD DISORDER

Several reports[95-97] indicated reductions in glial cell number in different areas of the brain in subjects with mood disorders and schizophrenia.

Glial fibrillary acidic protein (GFAP) is a major protein of astrocyte intermediate filaments and a specific marker for astrocytes[98,99]. While an increase in GFAP production may be a sign of astrogliosis, reactive injury and even neurodegeneration[100-102], a decrease in its levels may signify overall reductions in synaptic capabilities of neurons[96-103]. Fatemi et al.[102] investigated the production of GFAP by glial cells in mood disorders and SCZ reporting a significant reduction in the levels of GFAP in cerebella of subjects with MDD and nonsignificant reductions in BD and schizophrenia. Data on literature[96,97,104] also indicate that antipsychotics and mood stabilizers may have receptor sites on glial cells and can upregulate levels of GFAP potentially impacting neuronal health and stability[95,105].

DISCUSSION

Evidence coming from studies reporting an altered expression of SP4 and TrKB signaling in cerebellum of patients with mood disorders suggests the existence of neuro-plastic rearrangement phenomena leading to a progressive functional and structural modification. If this kind of alterations could be considered as a consequence of diaschisis phenomena involving prefrontal and limbic system or primarly starting from cerebellum is not already known.

Schmahmann and Sherman[16] since 1998 emphasized the critical role for the cerebellum in modulating fine aspects of emotional and cognitive function, just as it is postulated to play a key role in fine tuning motor function.

To the extent that cerebellar function is pathological in the direction of relative hyper-associativity with other regions of the brain in BD patients, it is possible to visualize this resulting in the loss of the normal modulation of mood leading to the production of more extreme emotional and behavioral swings, and possible over-corrections seen in both mania and depression.

This could be analogous to the abnormality seen in fine motor control where "past pointing" in the finger-to-nose test is associated with cerebellar lesions. This wealth of evidence from contemporary studies in patients indicating that the cerebellar vermis is engaged in the modulation of emotional processing, provides support for the clinical relevance of cerebellar-limbic connections, and is in agreement with earlier clinical[110] and electrophysiological studies8 in patients that led to the first indication of the cerebellum as an "emotional pacemaker"[107].

Even though many results from neuropsychiatric investigations documented abnormalities in cerebellar function and structure, there is no data showing whether these alterations of cerebellum are a risk factor for developing mood disorder or whether they are already present before the disease onset, or even a consequence of the disease.

Mills et al.[28] and Monkul et al.[29] performed some relevant studies on this issue. Mills et al.[28] reported that V3 volume was smaller in patients with multiple manic episodes compared to healthy controls, and that first-episode patients did not differ from healthy controls.

Monkul et al.[29] found an inverse correlation between age and vermis area V3 in bipolar patients, suggesting a more pronounced age-related decrease in vermis area V3 in young bipolar patients compared with healthy individuals.

Abnormalities of the cerebellar vermis may thus be present early in the course of BD and are possibly involved in the neuropathology of this disease as a neurodegenerative consequence of repeated episodes.

The reciprocal relationship between cerebellar and cortical activities has theoretical therapeutic implications for BD and MDD and new technologies are nowadays available to modify deep neuronal activity[108-112]. Recently, Schutter and van Honk[113] showed that single-pulse transcranial magnetic stimulation (TMS) over the posterior vermis increased frontal theta activity.

This finding highlighted the importance of the cerebellar vermis in human emotional functions. The role of the posterior vermis as the substrate for the putative limbic cerebellum is further substantiated by the finding that patients with cerebellar stroke involving vermian or paravermian regions have increased PET activation in prefrontal regions and decreased activation in limbic structures in response to unpleasant stimuli, and by the observation that the posterior vermis shows activation in substance abusers during reward-related tasks.

Cerebellar vermis activation have also been observed in neuroimaging studies investigating panic[114], sadness and grief[115].

Demirtas-Tatlidede et al.[116] conducted the first clinical trial to test whether enhancing cerebellar vermal activity using intermittent theta burst stimulation (iTBS) could be a safe non invasive method for augmenting the cerebellar modulation of the putatively dysfunctional neural networks in schizophrenia. In this study, eight treatment-refractory patients with SCZ underwent 10 sessions of iTBS to the cerebellar vermis using MRI-guided TMS.

The improvement observed in negative symptoms, mood and cognition represents an encouraging initial step towards treatment of refractory SCZ and potentially MDD and BD.

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