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Review article

The cerebellum under stress

Josep Moreno-Rius

Pharmacy El Toro, La Fuente 11, 12429 El Toro, Castellon, Spain

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ABSTRACT

Stress-related psychiatric conditions are one of the main causes of disability in developed countries. They account for a large portion of resource investment in stress-related disorders, become chronic, and remain difficult to treat. Research on the neurobehavioral effects of stress reveals how changes in certain brain areas, mediated by a number of neurochemical messengers, markedly alter behavior. The cerebellum is connected with stress-related brain areas and expresses the machinery required to process stress-related neurochemical mediators. Surprisingly, it is not regarded as a substrate of stress-related behavioral alterations, despite numerous studies that show cerebellar responsivity to stress. Therefore, this review compiles those studies and proposes a hypothesis for cerebellar function in stressful conditions, relating it to stress-induced psychopathologies. It aims to provide a clearer picture of stress-related neural circuitry and stimulate cerebellum-stress research. Consequently, it might contribute to the development of improved treatment strategies for stress-related disorders.

1. Introduction

Stress can be defined as a multi-level response of an organism when it faces an environmental challenge that is aimed at overcoming that difficulty. Prolonged periods of stress produce deleterious effects that might become chronic and/or life-threatening (McEwen et al., 2015). These effects are related to its involvement in medical conditions such as metabolic syndrome (Goldstein et al., 2016), cardiovascular disease (Kivimaki and Kawachi, 2015), type 2 diabetes mellitus (Hackett and Steptoe, 2017), allergies (Dave et al., 2011), and autoimmune diseases (Stojanovich and Marisalvjevich, 2008). Nevertheless, stress is not only involved in physical medical conditions. Indeed, brain disorders and functions are notably influenced by stress. Its role in precipitating psychiatric pathologies is either suggested or demonstrated for conditions such as mood disorders (Kendler et al., 1999), anxiety disorders (Weger and Sandi, 2018), and post-traumatic stress disorder (PTSD; Yehuda et al., 2015). Furthermore, neurodegenerative disorders are apparently precipitated or worsened by stress (Hemmerle et al., 2012; Hou et al., 2014; Machado et al., 2014; Mravec et al., 2018). Similarly, stress alters several cognitive functions like attention, memory, and cognitive flexibility (Liston et al., 2006; Graybeal et al., 2011; Shields et al., 2017). Therefore, the brain is considered to be one of the most stress-sensitive organs (McEwen et al., 2015), and this high sensitivity provides a biological substrate for the appearance of psychiatric disorders after continuous stress exposure. It is also noteworthy that the available treatment options for stress-induced psychiatric conditions are far from fully efficient. As a result, sustained remission is difficult to achieve, and relapse rates are very high (Yonkers et al., 2003; Kelsey, 2004).

The neural circuitry that governs stress-induced behavioral changes and stress-related disorders such as PTSD includes a series of cortical and subcortical brain structures, such as the hypothalamus (Buller, 2003; Bains et al., 2015), amygdala (McEwen, 2007; Rozendaal et al., 2009), hippocampus (Rozendaal et al., 2009; McEwen et al., 2016), prefrontal cortical areas (Rozendaal et al., 2009; McEwen et al., 2016), midbrain structures, e.g., the periaqueductal gray (PAG; Chou et al., 2018; Ho et al., 2018), raphe nuclei (Natarajan et al., 2017; Nishitani et al., 2019), and reward-related areas, including the ventral tegmental area (VTA; Solecki et al., 2017; Fernandez et al., 2018; Rabellino et al., 2018b) and the nucleus accumbens (NAc; Francis et al., 2015; Sussman et al., 2016; Chandra et al., 2017). Within these brain areas, a number of neurochemical mediators and their receptors modulate stress-induced behavioral changes. This action occurs for glucocorticoids (Jochems et al., 2015; Palma-Gudiel et al., 2015), corticotropin-releasing factor (CRF; Partridge et al., 2016; Dedic et al., 2018), norepinephrine (Wood and Valentino, 2017; Borodovitsyna et al., 2018), serotonin (Natarajan et al., 2017; Nishitani et al., 2019), and endocannabinoids (Hill and McEwen, 2010; Gunduz-Cinar et al., 2013), among others.

The cerebellum contains more neurons than the rest of the brain (Herculano-Houzel, 2009), and its contribution to several nonmotor domains is being increasingly recognized (Moreno-Rius, 2018, 2019a,

E-mail address: moreno210189@hotmail.com.

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2019b). Furthermore, it is connected to stress-related brain zones and expresses the neural machinery necessary for processing the chemical mediators involved in stress responses. However, literature and research on stress and its neurobehavioral consequences has paid little attention to the cerebellum until very recently (Rabellino et al., 2016; Tomas-Roig et al., 2016; Tomas-Roig and Havemann-Reinecke, 2018), despite several studies that reported cerebellar changes in response to stress in experimental animals and humans (Kitraki et al., 1999; Jastreboff et al., 2011; Babenko et al., 2012). A potential explanation for this lack of attention might relate to the traditional views of the cerebellum as a structure exclusively devoted to motor functions. This view is strongly ingrained in medical and biological curricula, owing to the vast number of studies that demonstrated a role for the cerebellum in several motor-related functions since the early 20th century. These reports encompass reflex movements (Brogden and Gantt, 1937; Moruzzi, 1950; Rowan et al., 2018), oculomotor control (Alahyane et al., 2008; Xu-Wilson et al., 2009; Baier and Dieterich, 2011), other types of motor learning (Yeo et al., 1985; Steiner et al., 2019), and speech production (Ackermann et al., 1999, 2007). It is thus possible that this view precluded considering stress-induced cerebellar changes as related to non-motor domains, an oversight that potentially underestimates the cerebellar contribution to the stress response.

Therefore, this work highlights the numerous studies that involve the cerebellum in the stress response and proposes a hypothesis for its role. To this end, a description of cerebellar anatomy and synaptic organization is provided first, followed by describing cerebellar connections with other stress-related brain areas. Subsequently, cerebellar changes induced by acute and chronic stress in non-human animals are reviewed. The studies that link cerebellar alterations with stressor exposure in humans are then discussed, including those performed in PTSD patients. Finally, a hypothesis to clarify the function that cerebellar changes might play in stress-induced behavioral changes is proposed. This work also aims to help guide future experimental approaches on the topic and establish the cerebellum as a part of the neural networks that underlie stress-related responses.

2. Cerebellar anatomy, internal circuitry, and connections to stress-related brain areas

The cerebellum consists of a central region called the vermis and two cerebellar hemispheres on each side of the vermis. Its midsagittal view shows white matter arborization called the arbor vitae surrounded by grey matter. Inside the white matter formation are three pairs of nuclei (Purves et al., 2001). The cerebellum is attached to the brainstem through three pairs of structures named cerebellar peduncles (inferior, middle, and superior). All cerebellar efferents and afferents pass through the peduncles to reach their respective targets. Macroscopically, the cerebellum is divided by two main transverse fissures. The primary fissure separates the anterior from the posterior lobe, and the posterior fissure separates the posterior lobe from the flocculonodular lobe (Purves et al., 2001). Moreover, the arrangement of the cerebellar cortical superficial fissures allows the identification of 10 different lobules (I-X), following an anteroposterior axis (Brodal, 1992). The anterior lobe comprises lobules I-V, the posterior lobe includes lobules VI-IX, and the flocculonodular lobe contains lobule X. Fig. 1 presents a representation of the cerebellar cortex and the domains each region is mostly involved in according to recent studies (Stoodley and Schachmann, 2009; Klein et al., 2016).

The cerebellar cortex's output projects to the deep cerebellar nuclei (DCN), which constitutes the output from the cerebellum to other brain areas. Following a lateral-medial axis, the names of the cerebellar nuclei are dentate (lateral in rodents), interposed, and fastigial. The dentate/lateral nuclei receive projections from the lateral parts of the hemispheres, the interposed nuclei receive them from paravermal zones, and the fastigial nuclei's input is the vermis.

Cerebellar cortical circuitry is highly stereotyped and does not

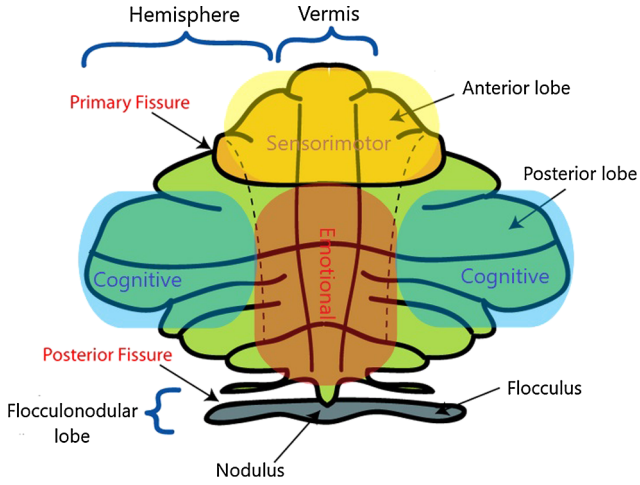

Fig. 1. Representation of macroscopic cerebellar view and association between cerebellar subregions and functions. The image represents an unfolded cerebellum, with shaded areas indicating the type of functions these subregions are predominantly (not exclusively) associated with. Adapted from a copyright-free image from Wikimedia Commons.

significantly vary by region. It is composed of three different layers, the most dorsal being the molecular layer. It contains Purkinje cell (PC) dendrites, different types of inhibitory interneurons, and parallel fibers (PF). These fibers represent the granule cell (GC) glutamatergic axons. Underneath, the PC layer contains PC somata and Bergmann glial cells. PCs represent the sole cerebellar cortex output. The most ventral layer, the granule cell layer, contains a large number of GCs, which are modulated by Golgi inhibitory interneurons, unipolar brush cells, and Lugaro neurons, as well as different types of glial cells (Purves et al., 2001).

Two main afferents constitute the cerebellar input. The mossy fibers (MF), which arise from the pontine nuclei, convey information from cerebral cortices, limbic areas, and the basal ganglia to the cerebellar cortex. These fibers target the glomerular formation at the granule layer and form synapses with GCs. Climbing fibers (CF) arise from the inferior olive and form synapses with PC dendrites and somata (Warren and Sawtell, 2016). Aside from PF activity, these two excitatory inputs modulate the PC GABAergic output onto DCN neurons, an action that modulates global cerebellar output. A schematic representation of the cerebellar synaptic organization is presented in Fig. 2.

As mentioned in Section 1, the cerebellum presents a variety of connections with other brain areas that are traditionally considered to mediate stress-induced behavioral alterations. Studies in non-human animals and resting-state functional connectivity magnetic resonance imaging analyses in human subjects support this assumption. This role is the case for cerebellar connections with the hypothalamus (Dietrichs, 1984; Zhu et al., 2006; Contreras-Rodriguez et al., 2017), hippocampus (Rochefort et al. 2011; Babayan et al. 2017; Choe et al., 2018), amygdala (Sang et al., 2012; Farley et al., 2016, 2018), prefrontal cortex (Tomasi and Volkow, 2011; Badura et al., 2018; Choe et al., 2018), PAG (Gonzalo-Ruiz et al., 1990; Koutsikou et al., 2014; Thome et al., 2017), raphe nuclei (Kaufman et al., 1996; Mierzejewska-Krzyzowska et al., 1996; Beliveau et al., 2015), VTA (Oades and Halliday, 1987; Ikai et al., 1991; Kline et al., 2016), and NAc (Cservenka et al., 2014; Holloway et al., 2019). Moreover, certain neurochemical messengers are also listed as mediators of stress-induced behavioral anomalies in Section 1. The cerebellum also expresses the cellular machinery necessary for interacting with those mediators, and altering those systems affects cerebellar physiology and function. This phenomenon applies to glucocorticoid (Sousa et al., 1989; Wilber et al., 2010) and CRF signaling (King et al., 1997; Wang et al., 2017), monoaminergic systems such as the serotonergic system (Arpin-Bott et al., 2006; Lippiello et al., 2016)

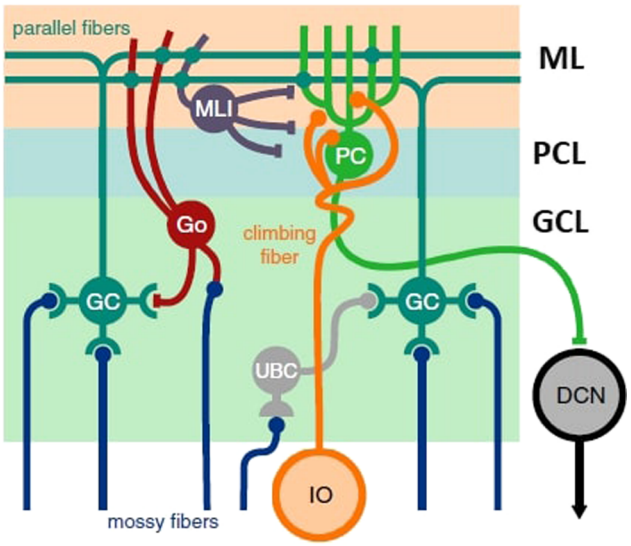

Fig. 2. Representation of cerebellar synaptic organization. Information reaches the cerebellar cortex through mossy and climbing fibers. There, multiple neurons receive this input and forward it directly or indirectly to Purkinje cells, which project to the deep cerebellar nuclei. The latter represent cerebellar output to efferent structures. DCN: Deep cerebellar nuclei; GC: Granule cell, GCL: Granule cell layer; Go: Golgi cell; IO: Inferior olive; ML: Molecular layer; MLI Molecular layer interneuron; PC: Purkinje cell; PCL: Purkinje cell layer; UBC: Unipolar brush cell. Adapted with permission from Warren and Sawtell (2016).

and the noradrenergic system (Schambra et al., 2005; Lippiello et al., 2015), and the endocannabinoid system (Herkenham et al., 1990; Rinaldo and Hansel, 2013).

The aforementioned anatomical and biochemical findings place the cerebellum in an ideal position to play a functional role in stress-induced neurobehavioral effects. Therefore, studies that assess stress-induced neural alterations might also report cerebellar changes when this brain area is included in the examinations. Works performed in non-human animals that describe those changes are discussed in Section 3.

3. The cerebellum and stressor exposure in non-human experimental animals

The study of the behavioral and neural effects of stress in rodents involves the use of paradigms in which a stimulus or stimuli known to elicit stress-like physiological responses (such as enhanced corticosterone levels) is/are applied. After stressor application, behavioral and/or neural stress effects are assessed by comparing changes in these measures in stressed and unstressed experimental subjects. However, stressors can vary greatly in type and exposure time. For writing coherence/study grouping purposes, “acute stressor exposure” refers to exposure that occurs in a single experimental session, whereas “repeated stressor exposure” relates to stressor exposure that occurs during more than one experimental session.

3.1. Effects of acute stressor exposure on the cerebellum

A summary of the studies that report changes in the cerebellum as a result of acute stressor exposure is presented in Table 1.

3.1.1. Neurotransmitter/neuromodulating systems and associated signaling molecules

To the best of the author’s knowledge, the first study that demonstrated cerebellar changes in response to a stressful experience was performed by Curzon and Green in 1971. They report that a 10-min immobilization episode reduces cerebellar levels of 5-hydroxyindoleacetic acid in male rats (Curzon and Green, 1971). This compound is a serotonin metabolite, a catecholamine involved in stress-related responses (see Section 1). Therefore, this result might indicate reduced cerebellar serotonin after stressor exposure. However, a subsequent study (also with male rats) that used longer exposure times and combined stressors (immobilization + water exposure) found the opposite patterns regarding the serotonergic system (Takada et al., 1995). The latter study is supported by a more recent investigation. In this report, a 1-hour episode of immobilization stress applied to mice is accompanied by increased serotonergic and noradrenergic precursors levels (Lee et al., 2012). No specification with regards to the animals’ sex is provided in this study.

Additional early studies found calcium alterations in the cerebellum in response to acute stressor exposure. Calcium mediates physiological properties of cerebellar neurons (Regehr and Alturi, 1995; Brown et al., 2004) and stress effects in other brain areas (Satoh et al., 2006). Exposure to a cold environment reduces calcium content in the cerebellum of male rats (Sabbot and Costin, 1974) and elevates calcium uptake in both rats and mice of unspecified sex (Watanabe et al., 1987). These results suggest stressor-induced calcium depletion in the cerebellum. However, the intricate cerebellar circuitry and different functions of cerebellar subregions make it difficult to establish further conclusions.

Other neurotransmitter systems also vary in the cerebellum in response to acute stress. The cholinergic system mediates physiological properties of cerebellar neurons (Takayasu et al., 2003; Rinaldo and Hansel, 2013) and stress-related neural effects outside the cerebellum (Mineur et al., 2013, 2016). With regards to this system, 15 min of forced swim exposure significantly increases muscarinic cholinergic receptor binding in male and female rats (Estevez et al., 1984), and immobilization in a cold room enhances cerebellar acetylcholinesterase levels in male rats (Tsakiris and Kontopoulos, 1993). Thus, it is possible that acute stress increases cerebellar cholinergic signaling through muscarinic receptor-dependent mechanisms, but further anatomical specificity cannot be inferred from these studies.

Acute stress also promotes glutamatergic alterations at the cerebellar level. Glutamate mediates stressor effects in many brain areas (Nasca et al., 2017; Montalban et al, 2019), and it is the neurotransmitter that controls cerebellar input and output (Purves et al., 2001). Cerebellar glutamatergic alterations after acute stressor exposure include increased NMDA receptor binding (Yoneda et al., 1994) and decreased radioactive glutamate uptake in male rats (Borisova et al., 2002). Therefore, these studies support that NMDA-mediated glutamatergic signaling can increase as result of acute stressor exposure.

Studies also note GABAergic system deregulations. GABA is the main neurotransmitter of PCs and other cerebellar interneurons, and it participates in the neural effects of stress (Jie et al., 2018). There is significant variability in studies that examine this neurotransmitter system. Different stressors, including forced swim (Park et al., 1993; Bitran et al., 1998), shocks (Drugan et al., 1989; Concas et al., 1993), and handling (Biggio et al., 1980, 1981), decrease $GABA_A$ receptor binding at different sites within the receptor. Most studies were conducted in males, but the one that was conducted in females (Bitran et al., 1998) report similar results. However, social defeat stress, a paradigm that consists of introducing an experimental mouse in the cage of a more dominant one that attacks the intruder (Miller et al., 1987; Barnhill et al., 1991), and surgical stress (Revilla et al., 1999) produce the opposite effects in male mice and rats, respectively. Whether the pattern of results is due to the different applied stressors or some other factor(s) is unclear and conclusions cannot be unequivocally established.

Acute hyperthermic stress increases dynorphin protein levels in the male rat cerebellum (Sharma and Alm, 2002). This endogenous opioid acts preferentially on kappa opioid receptors (Carroll and Carlezon, 2013). It mediates stress-induced behavioral alterations as well as drug-induced dysphoric-like effects (Bruchas et al., 2010), but its role in

Table 1
Animal studies describing effects of acute stressor exposure on the cerebellum.

Species (sex)	Stressor	Stressor features	Main results	Reference
Rat (male)	Immobilization	10-min episode	Decreased 5-HIAA levels	Curzon and Green, 1971
Rat (male)	Immobilization and cold	45–180 min immobilization at 4° RT	Increased acetylcholinesterase levels	Tsakiris and Kontopoulos, 1993
Rat (male)	Cold	30 min in cold water (4°)	Increased calcium uptake	Sabbot and Costin, 1973
Mouse (male)	Cold swim, heat, fight	ice-water swim: 30 sec; hot plate 56°: 20 sec; fight: 5–20 min	Increased cGMP content	Dinnendahl, 1975
Rat (male)	Footshocks	2-sec, 1.6-mA pulses delivered every 165 sec for 30 min	Decreased ATP, ADP levels	Dickman et al., 1973
Rat (unspecified)	Cold	30–120 min at 8° RT	Decreased calcium content	Watanabe et al., 1987
Mouse (male)	Cold swim	10 min in cold water (6°)	Decreased $GABA_A$ receptor binding (BZD site)	Park et al., 1993
Rat (male)	Tailshocks	80 5-sec, 1–2 mA tailshocks delivered every min	Decreased $GABA_A$ receptor binding (BZD site)	Drugan et al., 1989
Rat (male)	Footshocks	0.2 mA, continuous for 5 min	Decreased $GABA_A$ receptor binding (Cl^- entry site)	Concas et al., 1993
Rat (female)	Forced swim	5 min at ambient temperature	Decreased $GABA_A$ receptor density	Bitran et al., 1998
Rat (male)	Hypergravity	Centrifugation for 1 h at 10G	Decreased glutamate uptake	Borisova et al., 2002
Rat (male)	Immobilization	1–2 h long ± 1 h recovery	Decreased glucose utilization	Sung et al., 2009
Rat (male)	Handling	Animals unhabituated to the sacrifice manipulations	Decreased GABA receptor availability and affinity	Biggio et al., 1980, 1981
Rat (male)	Various	Variable	Increased thyroxin levels, decreased triiodothyronin levels	Baumgartner et al., 1998
Rat (male)	Cold	5 min at 4° RT with wetted fur	Increased cGMP levels	Biggio and Guidotti, 1976
Mouse (unspecified)	Immobilization	30-min episode	Increased allopregnanolone, 5α-dihidroprogesterone levels	Lee et al., 2016
Mouse (male)	Immobilization	30-min episode	Increased glutathione levels	Ghizoni et al., 2006
Mouse (unspecified)	Immobilization	30-min episode	Increased levels of monoamines, precursors and metabolites	Lee et al., 2012
Rat (male)	Immobilization	4 30-min episodes every 2 h in a single day	Reduced creatine levels	Herring et al., 2008
Rat (both)	Forced swim	15-min episode at 18°	Increased muscarinic cholinergic receptor binding	Estevez et al., 1984
Mouse (female)	Shaking	90-sec episode in rotatory bath shaker	Increased cGMP levels	Rubin and Ferrendelli, 1977
Rat (male)	Handling	Unhabituated animals to the sacrifice manipulations	Increased cGMP levels	Corda et al., 1980
Mouse (male)	Social defeat	Fighting episodes until intruder receives 100 bites	Increased $GABA_A$ receptor binding (BZD site)	Miller et al., 1987
Rat (male)	Footshock	5-sec, 0.5 mA shock	Increased cGMP levels	Sethy and Oien, 1991
Rat (male)	Immobilization and water exposure	3 h immobilization in water at ambient temperature (23°)	Increased levels of serotonin, metabolites and precursors	Takada et al., 1995
Rat (female)	Immobilization	10-min episode	Increased cGMP levels	Kant et al., 1981
Rat (both)	Immobilization	30-min episode	Increased blood–brain barrier permeability	Skultetyova et al., 1998
Rat (male)	Surgical stress	Placebo pellet implantation	Increased $GABA_A$ receptor binding (BZD site)	Revilla et al., 1999
Rat (both)	Forced swim	30-min episode at 30°	Increased blood–brain barrier permeability	Sharma et al., 1991
Mouse (male)	Earshock, earclip	8 mA, 1-sec shock, earclipping as in shocked animals with no shock	Increased c-fos mRNA expression	Daval et al., 1989
Rat (male)	Forced swim and immobilization	1 min swim at 23° and 15 min immobilization	Increased c-fos mRNA expression	Bozas et al., 1997
Rat (male)	Immobilization	60-min episode	Increased c-fos mRNA expression in the granule cell layer	Imaki et al., 1993
Mouse (male)	Social defeat	Fighting episodes until intruder receives 100 bites	Increased $GABA_A$ receptor binding (BZD site)	Barnhill et al., 1991
Rat (male)	Immobilization and water exposure	3 h immobilization in water at ambient temperature (25°)	Increased NMDA receptor binding	Yoneda et al., 1994
Rat (male)	Cold	60-min episode at 4-10° RT	Increased p75 receptor mRNA expression	Foreman et al., 1995
Mouse (male)	Immobilization	8-hour episode	Increased XBP1 splicing	Hosoi et al., 2019
Rat (male)	Hyperthermia	240-min exposure to room at 38°	Increased GFAP protein expression	Sharma et al., 1992
Rat (male)	Hyperthermia	240-min exposure to room at 38°	Increased dynorphin protein expression	Sharma and Alm, 2002

Table 2
Animal studies describing the effects of repeated stressor exposure on the cerebellum.

Species (sex)	Stressor	Stressor features	Animals' age	Main results	Reference
Rat (male)	Various	Chronic unpredictable mild stress, 3 exposure cycles	Unspecified	Decreased serotonin content and depressive-like behavior	Dubey et al., 2015
Mouse (male)	Various	Chronic unpredictable mild stress, 42 stressor exposures	Adulthood (8wk)	Decreased activity in fMRI scan and depressive-like behavior	Huang et al., 2017
Mouse (male)	Various	1 stressor exposure/day for 4 days	Adulthood (4–5 mo)	Decreased calcyclin protein expression	Bartkowska et al., 2017
Rat (both)	Restraint and tailshock	40 3-sec, 2 mA tailshocks every 140–180 s for 2 h while restrained, 3 days	6–7 wk	Decreased CB_1 mRNA expression	Xing et al., 2011
Rat (male)	Forced swim, restraint	Stressors applied alone or in combination for 8–14 days	Adulthood (3–4 mo)	Decreased Glucocorticoid receptor mRNA expression	Kitraki et al., 1999
Mouse (male)	Psychosocial	1-h exposure to a resident mouse for 21 days	Adulthood (7-8wk)	Decreased Neuregulin 1 mRNA expression	Tomas-Roig and Havemann-Reinecke, 2019
Rat (male)	Various	1 stressor exposure/day for 8 days	Adulthood (6 mo)	Decreased Sialyltransferase activity	Dabelic et al., 2004
Mouse (male)	Restraint and injection	Daily restraint-only or restraint and injection for 1 wk.	Unspecified	Decreased $GABA_A$ receptor binding (BZD site)	Mosaddeghi et al., 1993
Rat (male)	Restraint	20-min exposure for 14 days	4 mo.	Inccreased Adipoq, prolactin receptor mRNA levels	Babenko et al., 2012
Rat (male)	Restraint	Daily 150-min episode for 7 days	Unspecified	Increased Phenylethanolamine N-methyltransferase levels	Saavedra and Torda, 1980
Rat (male)	Various	Chronic unpredictable mild stress, 4-wk exposure	8 wk.	Increased glucose utilization (PET scan)	Van Laeken et al., 2018
Rat (male)	Various	Chronic unpredictable mild stress, 3-wk exposure	Unspecified	Increased c-fos expression DCN	Huguet et al., 2017
Rat (male)	Various	Chronic unpredictable mild stress, 5-wk exposure	Unspecified	Decreased zif268 mRNA expression, decreased PC firing, reversal of CUMS behavioral phenotype by cerebellar stimulation	Bambico et al., 2018
Rat (male)	Various	Chronic unpredictable mild stress, 2 stressors/day during 4 weeks	5 wk	Increased resting-state activity (fMRI), accompanied with depressive-like symptoms and memory impairments	Li et al., 2018
Rat (male)	Various	Chronic unpredictable mild stress, 40-day exposure	Adulthood	Decreased mitochondrial respiratory chain enzyme activity, reversed by ketamine administration	Rezin et al., 2008, 2009, 2010
Mouse (male)	Psychosocial	1-h exposure to a resident mouse for 21 days	Adulthood (7-8wk)	Decreased CB1 receptor mRNA and protein expression, decreased calreticulin and tenascin-R mRNA expression	Tomas-Roig et al., 2016
Mouse (male)	Social defeat	5-min physical defeat for 10 days	Adulthood	Increased cerebellar volume correlating with stress-induced social avoidance	Anacker et al., 2016
Rat (both)	Restraint	6-h episode for 7 days	GD 7–14	Decreased GC synapses, synaptophysin expression and GC diameter	Ulupinar and Yucel, 2005
Rat (both)	Restraint	6-h episode for 7 days	GD 7–14	Decreased number of PCs	Ulupinar et al., 2006
Rat (male)	Various	Chronic unpredictable mild stress, 11-day exposure	GD 9–20	Increased number of apoptotic cells	Ladefoged et al., 2004
Mouse (male)	Restraint	1-h episode for 7 days	GD 14–21	Dendritic PC atrophy	Pascual et al., 2010; 2015
Rat (both)	Forced swim	20-min episode, water temperature 32°, for 10 days	GD 10–20	Increased blood–brain barrier permeability	Gomez-Gonzalez and Escobar, 2009
Rat (male)	Maternal separation, handling	2-h maternal separation, 2 min handling for 21 days	PD 1–21	Increased β-adrenoreceptor binding, decreased agonist-stimulated cAMP levels	Baamonde et al., 1999; 2002
Rat (male)	Maternal separation	3-h maternal separation for 13 days	PD 2–14	Increased GluA1, GluA3 expression and basal activity levels	Kokubo et al., 2018
Rat (male)	Maternal separation	3-h maternal separation for 5 days	PD 5–10	Transient BDNF, TrkB expression increase	Miki et al., 2013; 2014
Monkey (both)	Peer rearing	Reared by peers instead of mothers for 6 months	First 6 mo. of life	Increased cerebellar vermis volume	Spinelli et al., 2009

cerebellar physiology and function remains virtually unstudied.

Cerebellar cyclic guanosine monophosphate (cGMP) levels are also sensitive to stressor exposure. cGMP-mediated signaling controls the behavioral effects of stress (Masood et al., 2009; Yazir et al., 2012; Xu et al., 2015) and PC firing (Hartell, 1994, 1996). Several stressors, such as fighting, forced swim, heat exposure (Dinnendahl, 1975), cold exposure (Biggio and Guidotti, 1976), restraint (Kant et al., 1981), shaking (Rubin and Ferrendelli, 1977), footshocks (Sethy and Oien, 1991), and handling (Corda et al., 1980) elevate cerebellar cGMP levels in mice and rats of both sexes. Hence, reduced cerebellar cortex output might occur due to acute stress.

3.1.2. Cerebellar activity measurements

A number of studies also provide evidence of cerebellar activation in response to acute stress. Those studies quantified the expression of transcripts/products of the c-fos gene. This gene is transcribed in neurons after action potentials are fired and is labeled as an immediate-early gene (IEG). Thus, it is used as an indirect indicator of neural activation (Curran and Morgan, 1995). c-fos expression is enhanced upon stressor exposure in other stress-related brain areas (Reznikov et al., 2008; Cohen et al., 2017; Sood et al., 2018). Several other stimuli, including psychostimulant administration (Klitenick et al., 1995; Stephenson et al., 1999) and experimental seizure induction (Toth et al., 2018), also increase c-fos expression in the cerebellum. Acute stressors, like shocks applied in the ears, earclipping procedures (Daval et al., 1989), and immobilization (Imaki et al., 1993), upregulate c-fos mRNA expression throughout the granule cell layer of male rodents. Forced swim plus immobilization also elevates total cerebellar c-fos mRNA in male rats as assessed by northern blot assays (Bozas et al., 1997). The use of positron emission tomography (PET) scan, another technique aimed at measuring neural activity, produced different results. In this case, restraint stress decreases cerebellar glucose utilization in male rats (Sung et al., 2009). Methodological factors, including different spatial resolution of the techniques, might account for the divergence in the results. In line with this last report, acute stress-induced cerebellar metabolic slowdown is also supported by reductions in adenosine triphosphate (ATP) and adenosine diphosphate (ADP) that are caused by exposing male rats to inescapable foootshocks (Dickman et al., 1973).

3.1.3. Additional studies

Studies also report altered cerebellar hormone levels upon acute stressor exposure. This phenomenon occurs for thyroid hormones in male rats (Baumgartner et al., 1998) and progesterone derivatives in mice of unspecified sex (Lee et al., 2016). In the former study, l-thyroxin levels are reduced, and the levels of its active metabolite (3,3′,5-triiodo-L-thyronine) increase. The latter work reports elevated allopregnanolone and dihydroprogesterone levels. Some of these hormones may control certain brain function parameters (Timiras et al., 1955), and are involved in cognition (Smith et al., 2002), emotion (Bäckström et al., 2014; Schüle et al., 2014), and reward (Vallée et al., 2014). Given the cerebellar involvement in these functions (Moreno-Rius, 2018, 2019a, 2019b), stress-induced impairments on any of those domains could be mediated by these hormones at the cerebellar level.

Stress also alters cerebellovascular permeability. Immobilization (Skultetyova et al., 1998) and forced swim exposure (Sharma et al., 1991, 1995) increase blood-brain barrier permeability in rats of both sexes. Similar neurovascular effects from acute stress are reported for stress-related brain areas in the aforementioned studies and additional ones (Menard et al., 2017; Xu et al., 2019). Moreover, acute hyperthermic stress increases glial fibrillary acidic protein expression in the cerebellum of male rats (Sharma et al., 1992). Altogether, these studies indicate potential damage in the cerebellum even after acute stress.

Finally, additional findings that describe the cerebellar effects of acute stress include an increase in the neurotrophin receptor p75 levels in male rats (Foreman et al., 1995). This receptor is involved in neural death, regeneration, and associated disorders (Dechant and Barde, 2002). Acute stress also alters glutathione levels (Ghizoni et al., 2006), a peptide with recognized antioxidant properties. Enhanced XBP-1 gene splicing also occurs in male mice (Hosoi et al., 2019), and acute stressor exposure reduces cerebellar creatine levels in male rats (Herring et al., 2008). Creatine participates in brain cell metabolism, and its levels are altered in PTSD (Harnett et al., 2017). It is apparently beneficial for cognitive and mood disturbances when given as a supplement (Turner et al., 2015; Pazini et al., 2016), so it might have positive effects in patients afflicted from stress-related disorders.

3.2. Effects of repeated stressor exposure on the cerebellum

Repeated stressor exposure also causes marked effects on different cerebellar parameters, often accompanied by behavioral symptoms that resemble those of stress-induced psychopathologies in human beings. The studies are summarized in Table 2.

3.2.1. Neurotransmitter/neuromodulating systems and associated signaling molecules

One of these studies reports decreased cerebellar glucocorticoid receptor mRNA expression after applying forced swim and/or restraint to male rats for 8–14 days (Kitraki et al., 1999). Some of the neurotransmitter systems involved in acute stress-induced cerebellar alterations also present changes with repeated stressor exposure, including GABAergic transmission. One week of a daily restraint or restraint plus an injection episode decreases cerebellar $GABA_A$ receptor binding in male mice (Mosaddeghi et al., 1993). Similarly, three weekly chronic unpredictable mild stress (CUMS) cycles, which consist of daily stressor application to male rats, induces depressive-like behavior and a concomitant decrease in cerebellar serotonin content (Dubey et al., 2015). CUMS paradigms apply several stressors during a relatively long period of time in such a way that the animal cannot predict their order of appearance, thereby making the procedure more stressful for the experimental subjects.

With respect to catecholamines, an early study found increased levels of phenylethanolamine N-methyltransferase, an enzyme responsible for the conversion of norepinephrine to epinephrine, after seven daily, 2.5-hour restraint sessions were applied to male rats (Saavedra and Torda, 1980). Additionally, a study reported decreased CB_1 receptor mRNA expression in the cerebellum of male mice after 21 days of psychosocial stress (Tomas-Roig et al., 2016). This paradigm is similar to the aforementioned social defeat paradigm, except full physical contact cannot occur between mice. Given that the experimental mouse is placed inside a small cage while in the resident's home cage, physical contact is minimal, and the stress source in this paradigm is sensory cues provided by the resident mouse. This paper also reported decreased tenascin-R and calreticulin transcript levels. Tenascin-R is an integral component of perineuronal nets, extracellular structures that play important roles in brain physiology and functions (Xue et al., 2014; Carbo-Gas et al., 2017). Calreticulin is a calcium-binding protein that is highly expressed in the cerebellum, and it is sensitive to other stimuli such as methamphetamine (Hayashi et al., 2010) and prolonged stress exposure (Wen et al., 2015) in different brain areas. A recent report shows decreased calcyclin levels in the cerebellum of male mice (Bartkowska et al., 2017). This calcium binding protein is involved in aging and neurodegenerative disorders (Tiu et al., 2000; Hoyaux et al., 2002), but it was not previously linked to stress or its associated psychiatric conditions.

3.2.2. Cerebellar activity measurements

A number of studies also manifest alterations in cerebellar activity in response to repeated stressor application. Male mice that underwent a CUMS paradigm with 42 total stressor exposures show depressive-like behavior that is accompanied by cerebellar vermis deactivation (Huang

et al., 2017). However, in a subsequent study performed in male rats, CUMS paradigm exposure causes depressive-like behaviors and memory impairments and increases resting-state activity measures in the cerebellar hemispheres (Li et al., 2018). Similarly, a PET experiment conducted in male rats subjected to a 4-week CUMS paradigm found increased cerebellar hemispheric activity, yet this study reported no depressive-like symptoms (Van Laeken et al., 2018).

Other studies measured brain activity via quantifying IEG expression. c-fos expression increases in the deep cerebellar nuclei of male rats subjected to 3-week CUMS (Huguet et al., 2017). Furthermore, 5-week CUMS decreases zif268 expression throughout the cerebellar cortex of male rats, which is accompanied by reduced PC firing. Importantly, this work demonstrated that cerebellar vermis stimulation can reverse the depressive phenotype induced by CUMS, a finding that highlights the therapeutic promise of neuromodulatory interventions that target the cerebellum (Bambico et al., 2018).

3.2.3. Effects of early-life stress on the cerebellum

In addition to these studies, where stressor exposure took place during adulthood or, exceptionally, late adolescence (see Table 2), stressor application at early developmental time points also provokes structural and functional alterations in the cerebellum. Prenatal stress markedly affects cerebellar architecture, since restraining dams for 6 h from gestational day (GD) 7–14 reduces PC counts, average GC diameter, and GC synaptic contacts in 30-day-old pups of both sexes (Ulupinar and Yucel, 2005; Ulupinar et al., 2006). Reduced PC arborization is also evident in male pups aged 22 and 52 days when restraint sessions are shorter (1 h) and applied from GD 14–21 (Pascual et al., 2010, 2015). Moreover, increased blood-brain barrier permeability caused by ten, 20-min forced-swim episodes applied to the dams from GD 10–20 is apparent in 20-day-old pups (Gomez-Gonzalez and Escobar, 2009). This data supports the assumption that prolonged prenatal stress induces different kinds of tissue damage in the cerebellum.

Early postnatal stressor application is also responsible for a series of changes in cerebellar structure and function. In monkeys of both sexes, being reared by peers instead of mothers is associated with increased cerebellar vermis volume at 2–2.5 years of age (Spinelli et al., 2009). In rats, 2 h of maternal separation and 2 min of handling applied to male pups from postnatal day (PD) 1–21 increases cerebellar β-adrenoreceptor binding concomitant with decreased agonist-stimulated cAMP production at 1 and 3 months of age (Baamonde et al., 1999, 2002). These results indicate stress-induced decreased β-adrenoreceptor function.

Additional findings include enhanced expression of AMPA receptor subunits GluA1 and GluA3 after 13 sessions of maternal separation applied from PD 2–14, accompanied by increased cerebellar activity as assessed by local field potentials, both evident at 2–2.5 months of age (Kokubo et al., 2018). Further, in male pups, transient increases (present at PD 16 but absent at PD 30) in the levels of brain-derived neurotrophic factor and its receptor occur after maternal separation from PD 5–10 (Miki et al., 2013, 2014).

3.2.4. Additional studies

Further findings include decreased cerebellar neuregulin-1 mRNA expression in male mice after 3 weeks of psychosocial stress (Tomas-Roig and Havemann-Reinecke, 2019). Neuregulin-1 is a cellular adhesion protein encoded by the schizophrenia candidate gene NRG1. Neuregulin-1 modulates certain stress effects (Dang et al., 2016; Clarke et al., 2018) and also controls the expression of different receptor subunits in the cerebellum (Ozaki et al., 1997; Xie et al., 2004). Therefore, stress-induced neuregulin-1 expression and cerebellar receptor availability/expression changes might be related.

Daily social defeat episodes applied to male mice for 10 days enhance cerebellar volume, an alteration that is correlated with stress-induced social avoidance (Anacker et al., 2016). Intriguingly, applying a CUMS paradigm reduces mitochondrial respiratory chain enzyme levels in the cerebellum of male rats, and such alterations are reversed by administration of the fast-acting antidepressant ketamine (Rezin et al., 2008, 2009, 2010). Potential implications in stress-induced behavioral impairments might be difficult to envision, but it is not possible to discard a role for these enzymes in stress-induced cognitive alterations, owing to the described role of the mitochondria in cognitive functions such as memory (Hebert-Chatelain et al., 2016).

Application of various stressors for 8 days to male rats reduces cerebellar sialyltransferase levels (Dabelic et al., 2004). This enzyme is responsible for adding sialyl groups to certain biomolecules, a process that is necessary for proper brain architecture, myelination, and motor and cognitive function (Yoo et al., 2015). Alterations in hormone-mediated signaling also occur after repeated homotypic stress. Exposing male rats to 2 weeks of daily 20-minute restraint sessions reduces cerebellar adiponectin and prolactin receptor mRNA levels (Babenko et al., 2012). Besides their respective metabolic and bonding/attachment functions, neural signaling mediated by these mechanisms governs a handful of processes that are potentially relevant for stress-induced pathologies. Recent studies show a role for adiponectin in stress-induced behavioral alterations and the activity of stress-related brain areas (Guo et al., 2017; Zhang et al., 2017; Sun et al., 2019), and prolactin counteracts adrenocorticotropic hormone secretion and modulates stress-induced responses (Torner et al., 2001; Donner et al., 2007). Thus, these studies indicate a potential pathway through which cerebellar hormone-mediated signaling can influence stress behavioral effects.

Collectively, these studies provide abundant evidence of cerebellar changes in response to stress, at every developmental time point where stressor exposure occurred, and when stressors are acutely or repeatedly applied to non-human experimental animals. Therefore, neuroimaging assessments of human brain responses to stress-inducing stimuli and/or subjects who underwent markedly stressful events should involve the cerebellum. Those studies are discussed in Section 4.

4. The cerebellum and stress in humans

4.1. Cerebellar reactivity to stress-inducing stimuli in human subjects

The first type of studies discussed in this section involve the assessment of brain reactivity to the presentation of stress-inducing stimuli, such as scripts that describe highly stressful situations. These activation patterns are then compared to those elicited by a non-stressing script, and the areas that exhibit significant differences are considered to be involved in the stress response. A summary of the studies that report significant cerebellar differences using this method is presented in Table 3.

In healthy men and women, a personalized script-driven stress-inducing imagery session causes cerebellar activation in medial regions that expands laterally (Jastreboff et al., 2011; Seo et al., 2011). Another study replicated the previous finding, but between-sex assessment of these patterns revealed cerebellar hyper-responsivity in females when compared to males (Seo et al., 2017). These differential responsivity patterns might indicate the relative propensity of each sex to develop physical (e.g. coronary heart disease in males) versus psychiatric disorders (depression in females), both of which may appear upon prolonged stress conditions. This assumption is supported by the notable sex bias observed in epidemiological data for both types of conditions (Albert, 2015; Mozaffarian et al., 2015).

Further studies that assessed the temporal pattern of brain responses to stressful imagery sessions indicate medial cerebellar activity is more prominent in late versus early phases of the procedure in subjects of both sexes (Sinha et al., 2016). An evaluation of adolescents instead of adults with a similar procedure (Hommer et al., 2013) again found augmented cerebellar activity when comparing the stressful versus relaxing scripts effects. In this case, the maximum peak is located in the

Table 3
Studies describing cerebellar reactivity to stress-inducing stimuli in human subjects.

Experimental subjects	Procedural details	Cerebellar region	Main results	Reference
Healthy (overweight and lean) adults (47.9% females)	Exposure to stress, alcohol or neutral cues	Posterior lobe, medial	Increased fMRI signal stress > relaxing cues, independent of obesity-related factors	Jastreboff et al., 2011
Healthy adults (53% females)	Exposure to stress, alcohol or neutral cues	Posterior lobe, medial	Increased fMRI signal stress > relaxing cues	Seo et al., 2011
Healthy adults (42.7% females)	Exposure to stress or neutral cues	Anterior and posterior, medial	Widespread increased fMRI signal stress > relaxing cues, further increase females > males when analyzing the same cue contrast	Seo et al., 2017
Healthy individuals (37% females)	Exposure to stress or neutral cues	Posterior lobe, lateral, right hemisphere	Increased fMRI signal stress > relaxing cues when comparing late > early cue presentations	Sinha et al., 2016
Healthy adolsencents (37.2% females)	Exposure to stress, food or neutral cues	Posterior lobe, lateral, right hemisphere	Increased fMRI signal stress > relaxing cues	Hommer et al., 2013
Cocaine-dependent men with or without childhood abuse history	Exposure to stress, cocaine or neutral cues	Posterior lobe, lateral, right hemisphere	Increased fMRI signal stress > relaxing cues	Elton et al., 2015
Cocaine-dependent subjects (46.7% females) genotyped for a KOR gene polymorphism	Exposure to stress, cocaine or neutral cues	Medial, anterior-posterior transition zone	Increased fMRI signal stress > relaxing cues	Xu et al., 2013
Adolescents with or without prenatal cocaine exposure (36.4% females)	Exposure to stress, food or neutral cues	Posterior lobe, lateral, right hemisphere	Increased fMRI signal stress > relaxing cues in prenatally exposed individuals, not seen in non-prenatally exposed ones	Yip et al., 2014
Smokers and matched controls (41% females)	Exposure to stress, food or neutral cues	Posterior lobe, medial	Decreased intrinsic connectivity smokers < controls upon stress cue presentation	Garrison et al., 2016
Smokers and matched controls (30.4% females)	Exposure to stress or neutral cues	Multiple locations	Correlation between stress reactivity and smoking reduction	Kober et al., 2017
Healthy adults differing on traumatic life experiences (33% females)	Exposure to stress or neutral cues	1) Medial-anterior and posterior 2)anterior-posterior lateral, right hemisphere	Increased fMRI signal stress > relaxing cues location 1, correlation with trauma scores location 2	Seo et al., 2019
Healthy adults differing on traumatic life experiences (30.7% females)	Exposure to stress or neutral cues	Anterior, lateral, left hemisphere	Increased fMRI signal stress > relaxing cues	Seo et al., 2014

hemisphere and extends towards medial zones. These studies present the first evidence for cerebellar reactivity to stress in humans in motion-restricted conditions.

This cerebellar response is also observed in research that includes populations with psychiatric conditions who suffered stressful life events. Cocaine-dependent men, who did or did not experience childhood maltreatment, exhibit increased cerebellar hemispheric activation towards stressful stimuli (Elton et al., 2015). In another sample of cocaine-dependent individuals of both sexes, a single-nucleotide polymorphism in the kappa opioid receptor gene is associated with enhanced cerebellar response towards stress-related cues. Carriers of this variant also present greater cocaine craving and risk of relapse (Xu et al., 2013). Prenatal cocaine exposure also affects cerebellar responsivity to stressful stimuli, in such a way that prenatally-exposed men and women manifested enhanced cerebellar hemispheric activation upon stress-inducing stimuli presentation (Yip et al., 2014). Additional studies in smokers also support the cerebellar involvement in stress reactivity. Intrinsic connectivity of the medial cerebellum is lower in smokers than nonsmokers of both sexes when comparing reactivity between stress and neutral cues (Garrison et al., 2016). A subsequent study showed that cerebellar reactivity to stress cues predicts successful smoking reductions after treatment and at follow-up in smokers of both sexes (Kober et al., 2017). The findings of the latter study provide a link between psychiatric symptom improvement and cerebellar changes, a phenomenon that also appears in studies that will be discussed in the following subsections.

Finally, the assessment of brain responsivity towards stress-inducing stimuli as a function of previous trauma exposure showed that the medial cerebellum of trauma-exposed and non-trauma-exposed men and women is responsive to such stimuli. However, only trauma-exposed individuals present positive correlations between stress-induced cerebellar activity and basal cortisol levels as well as traumatic event exposure (Seo et al., 2019). This cerebellar stress responsivity-life adversity relationship is also evident in a previous study that quantified brain responses to those stimuli as a function of different life adversities in subjects of both sexes (Seo et al., 2014).

4.2. Morphological and functional cerebellar changes related to stressful life experiences and stress-induced task performance impairments

In addition to some studies discussed in Section 4.1, there are a number of additional investigations that reveal cerebellar morphological and functional changes as a function of stressful life experiences, but they do not involve direct presentation of stress-related stimuli (see Table 4).

Relative to this matter, the first study that demonstrated cerebellar anomalies found abnormal blood flow in the cerebellar vermis of men and women with a history of childhood sexual abuse (Anderson et al., 2002). Volumetric changes were also detected. Psychopathology-devoid adolescents of both sexes exposed to childhood maltreatment show negative correlations between grey matter volume in medial and lateral cerebellar zones and physical neglect as well as total trauma scores (Edmiston et al., 2011). Similarly, a subsequent study noted widespread cerebellar gray matter losses in adolescents of both sexes who reported experiencing early-life adverse events (Walsh et al., 2014). A recent investigation assessed the effect of childhood abuse on brain structure and reported reduced bilateral cerebellar volume in abused men and women compared to healthy controls (Lim et al., 2018). Interestingly, significant cerebellar volumetric alterations are also apparent when groups of patients with psychiatric disorders are compared. In men and women with a first-episode major depressive disorder (MDD), childhood maltreatment is associated with increased grey matter volume in the cerebellar vermis (Yang et al., 2017). Moreover, obsessive-compulsive disorder (OCD) patients who suffered stressful life events before disease onset present enhanced cerebellar hemispheric volume when compared to sex-matched, non-stressed patients or healthy controls

Table 4
Studies describing cerebellar changes as a result of stressful life experiences or stress-induced performance impairments associated with cerebellar changes in human subjects.

Experimental subjects	Procedural details	Cerebellar region	Main results	Reference
Healthy adults with or without childhood sexual abuse history (70.9% females)	Resting state fMRI	Medial	Increased relaxation time abused > non-abused	Anderson et al., 2002
Adolescents with or without childhood maltreatment history (50% females)	Grey matter volume analysis	Posterior lobe, medial and lateral	Correlation between grey matter losses and physical neglect and total trauma scores	Edmiston et al., 2011
Adolescents with or without childhood adversity history (60.3% females)	Grey matter volume analysis	Anterior and posterior, medial and lateral	Decreased grey matter volume childhood adversity < non-childhood adversity	Walsh et al., 2014
Adolescents with or without childhood abuse history (28% females)	Grey matter volume analysis	Bilateral	Decreased grey matter volume abused < non-abused	Lim et al., 2018
MDD patients and controls with or without childhood maltreatment (72.6% females)	Grey matter volume analysis	Anterior lobe, medial	Increased grey matter volume maltreated patients > non-maltreated patients	Yang et al., 2017
OCD patients with or without stressful life experiences and healthy controls (47% females)	Grey matter volume analysis	Posterior lobe, lateral, right hemisphere	Increased grey matter volume patients with stressful experiences > healthy controls	Real et al., 2016
OCD patients with or without stressful life experiences and healthy controls (47.8% females)	Grey matter volume analysis	Bilateral, anterior-posterior	Association grey matter volume increase-physical neglect experience in patients with stressful experiences	Brooks et al., 2016
Subjects with or without early life stress history (59.3% females)	Functional connectivity MRI	Posterior lobe, medial	Decreased functional connectivity early life stress-exposed < controls with the inferior parietal lobule	Philip et al., 2013
Methamphetamine-dependent individuals with differing childhood maltreatment history (46.7% females)	Functional connectivity MRI	Anterior/posterior, lateral, right hemisphere	Positive correlation between childhood maltreatment severity and cerebellum-amygdala functional connectivity	Dean et al., 2014
Healthy individuals with differing childhood adversity history (60.9% females)	Theory of mind task	Anterior lobe, medial	Correlation between reduced activity during theory of mind task and childhood adversity scores	Vai et al., 2018
Adolescents with differing traumatic life experiences (37.5% females)	Exposure to stress, food or neutral cues	Various locations	Decreased fMRI signal when viewing relaxing cues trauma-exposed < non-trauma exposed	Elsey et al., 2015
MDD patients and controls differing on traumatic life experience history (30.7% females)	Resting state fMRI	Posterior lobe, bilateral	Positive correlation between resting-state brain acticity and childhood trauma scores, bilateral in control, left hemisphere in patients	Du et al., 2016
Female MDD patients differing on previous stressful experience history	Exposure to pictures with emotional content	Unspecified	Increased activity patients with stress history > non-stressed patients	Li et al., 2016
Male cocaine-dependent individuals with differing abuse history	Exposure to drug, sex or neutral cues	Anterior lobe, lateral, left hemisphere	Increased activity abuse-exposed > non-abuse-exposed when comparing drug > neutral cues.	Regier et al., 2017
Burn-out subjects and healthy controls (57% females)	Functional connectivity MRI	Various locations	Increased functional connectivity between amygdala and cerebellum in burn-out subjects > controls	Golkar et al., 2014
Healthy individuals with or without prior experimental stress induction (56.3% females)	Oculomotor adaptation task	n/a	Stress-induced acquisition impairment of oculomotor adaptation response	Gheorghe et al., 2018
Healthy individuals with or without prior experimental stress induction (50.9% females)	Eyeblink conditioning	n/a	Stress-induced acquisition impairment of the conditioned eyeblink response	Wolf et al, 2009
Healthy men with or without prior experimental stress induction	Eyeblink conditioning	n/a	Stress-induced acquisition impairment of the discriminative stimulus properties of a cue predicting the CS+	Wolf et al, 2012

(Real et al., 2016). Likewise, cerebellar hemispheric enlargement occurs in OCD-afflicted men and women compared to controls, and it positively correlates with the experienced physical neglect in the patient group (Brooks et al., 2016).

Nevertheless, neuroimaging parameters other than grey matter estimations also change in the cerebellum as a function of early stressful experiences. Philip et al. (2013) found that men and women exposed to early life stress present decreased functional connectivity of the medial cerebellum with the inferior parietal lobule, a cortical area involved in sensory processing. Methamphetamine-dependent men and women with a history of childhood maltreatment present increased functional connectivity between the cerebellar hemispheres and amygdala when compared to non-maltreated subjects (Dean et al., 2014). Furthermore, early-life adverse experiences reduce cerebellar activation in a task that assesses the ability to infer the mental states and intentions of others (Vai et al., 2018). Similarly, adolescents of both sexes with a history of childhood trauma display broad cerebellar deactivation as a response to relaxing images when brain activity patterns are compared to control subjects (Elsey et al., 2015). Consistently, activity in the cerebellar hemispheres of MDD patients of both sexes in resting-state conditions correlates positively with the subjects' scores on a childhood trauma questionnaire (Du et al., 2016). An evaluation of brain responses from female MDD patients towards a picture with negative emotional content as a function of stressful life events mentions the left cerebellar hemisphere is significantly more active in patients who experienced stress. However, neither images nor statistical analyses that included the cerebellum in between-group comparisons are provided (Li et al., 2016). Furthermore, a study that assessed brain responses in cocaine-dependent men towards cocaine-related cues as a function of previous history of emotional, physical, and/or sexual abuse revealed enhanced cerebellar response towards cocaine-related versus neutral cues in the abuse-exposed group (Regier et al., 2017). Likewise, a comparison of subjects who suffered marked symptoms of occupational stress and healthy sex-matched controls noted increased functional connectivity between bilateral amygdalae and several spots within the cerebellum, including the vermis and parts of the anterior lobe (Golkar et al., 2014).

Additional findings that relate the cerebellum and stress in humans include the described stress-induced performance impairment in a saccadic adaptation task in subjects of both sexes (Gheorghe et al., 2018). This task consists of changing the position of a visual target at the onset of the saccadic movement in such a way that the subject is unable to initially perceive the target displacement. However, after several training trials, the subject can predict the target displacement, and the saccadic movement positions the eye towards the visual target (McLaughlin, 1967). This task is considered to be cerebellum-dependent because several studies performed in rodents and humans demonstrated a role for this brain area in saccadic eye movement adaptation (Takagi et al., 1998; Robinson et al., 2002; Panouilleres et al., 2013). Similarly, stress-induced performance impairments were also described in a different type of cerebellum-dependent learning paradigm, namely the eyeblink conditioning paradigm. It consists of making the experimental subject associate an eye-directed, blink-eliciting air puff with a sound by repeatedly presenting them together. After a number of pairings, the presentation of the sound alone elicits the eyeblink response (Bracha, 2004). This task is considered to be cerebellum-dependent because several decades of research indicated a crucial role for the cerebellum (Yeo et al., 1985; Li et al., 2019; Steiner et al., 2019). In this regard, experimental stress induction impairs the acquisition of this conditioned response in men and women (Wolf et al., 2009, 2012). Besides, increased functional connectivity of the hippocampus with the cerebellar vermis and left hemisphere in healthy subjects pre-exposed to stress compared to unstressed ones occurs when they perform a semantic categorization task (Vogel et al., 2018).

Collectively, these studies demonstrate that stressful stimuli or experiences are associated with a number of changes in the cerebellum in healthy individuals as well as in psychiatric populations. Based on this evidence, it is also feasible to assume that patients afflicted with PTSD, the prototypical chronic stress disorder, will also present them. The studies that describe those changes are discussed in the next subsection.

4.3. Cerebellar changes associated with PTSD

PTSD is a condition characterized by vividly re-experiencing a traumatic episode that results in significant impairments in cognitive, emotional, and social/interpersonal domains. Like in many other psychiatric conditions, the individual symptomatology of two PTSD patients can be fundamentally different, but the subjects present the same diagnosis. Nonetheless, the trigger for the pathology is always an extremely stressful situation, and consequences of re-experiencing the situation such as intrusions, avoidance behaviors, and associated physiological alterations are qualitatively similar to intense non-traumatic direct stressors. Therefore, potential findings that involve the cerebellum in PTSD might also support general conclusions about its participation in the neural stress response. An early publication that suggested this PTSD-cerebellum link, however, was not a neuroimaging study. It was a case report that described an altered sense of time right after a motor vehicle accident, as well as intrusions and spatial memory issues months after the traumatic event. The authors suggest cerebellar involvement in PTSD because of the role of the cerebellum in time perception and the initial findings that related cerebellar function to spatial processing (Ursano and Fullerton, 1999). Consistent with this idea, numerous studies reported structural and functional alterations in the cerebellum of PTSD patients, which are summarized in Table 5.

The first of these works assessed cerebellar volumes in children of both sexes with PTSD or generalized anxiety disorder and healthy controls. Total, left, and right cerebellar volumes are reduced in PTSD-suffering children when compared to the generalized anxiety and healthy control groups (De Bellis and Kuchibhatla, 2006). Moreover, the traumatic experience age-of-onset and trauma duration correlate with cerebellar volumes. Specifically, trauma age-of-onset and right and left cerebellar volumes are positively correlated. On the other hand, right and total cerebellar volumes correlate negatively with trauma duration. A subsequent study from the same group showed these differences to be mainly driven by grey matter volume decreases in the cerebellar hemispheres, yet there is a trend towards significant vermis grey matter reduction (De Bellis et al., 2015). This study also reported a negative correlation between cerebellar grey matter and PTSD symptom scores, findings that indicate potential involvement in the maintenance of the disorder. A distinct morphometry study that assessed changes in PTSD-suffering boys and girls noted reduced total cerebellar vermis volume (mainly driven by posterior vermis volume reductions; Carrion et al., 2009).

In line with these findings obtained from children, adult populations also present cerebellar volume reductions. Specifically, the vermis and left hemisphere volumes decrease when comparing men and women diagnosed with PTSD with trauma-exposed, PTSD-free controls. Cerebellar volume also correlates negatively with the PTSD symptom checklist scores in these subjects (Baldaçara et al., 2011, 2012). This volume reduction is also significant for the left hemisphere when PTSD patients are compared with sex-matched OCD-afflicted individuals (Cheng et al., 2015). However, a later investigation performed in PTSD-suffering Canadian soldiers provided apparently contradicting data with the aforementioned literature, since the posterior hemisphere volume is greater than that of PTSD-free soldiers (Sussman et al., 2016).

Studies that assess basal brain activity patterns in PTSD-suffering individuals reinforce the notion of cerebellar participation in PTSD. An initial single-photon emission computed tomography (SPECT) study found several spots with increased glucose utilization in the left cerebellar hemisphere of PTSD-afflicted individuals of both sexes when compared with trauma-exposed individuals and healthy controls (Bonne et al., 2003). The cerebellar hemispheres of war-related PTSD patients are also significantly more active in basal conditions when

Table 5
Studies describing cerebellar changes in PTSD patients.

Experimental subjects	Procedural details	Cerebellar region	Main results	Reference
Children-adolescent PTSD patients, GAD patients and healthy controls (47.9% females)	Grey matter volume analysis	Medial and lateral, left and right	Decreased medial left and right cerebellar volume PTSD < GAD and controls	De Bellis and Kuchibhatla, 2006
Children-adolescent PTSD patients, PTSD-free maltreated individuals and healthy controls (53.8% females)	Grey matter volume analysis	Posterior lobe, medial and lateral	Reduced cerebellar grey matter in total cerebellum and left and right posterior hemispheres in PTSD patients < maltreated without PTSD and controls, correlation between volume reductions and PTSD symptoms	De Bellis et al., 2015
Children PTSD patients and controls with subthreshold PTSD symptoms (41.7% females)	Grey matter volume analysis	Posterior, medial	Decreased grey matter volume PTSD patients < controls in the vermis, mostly influenced by posterior vermis volume reductions	Carrion et al., 2009
PTSD patients and trauma-exposed, PTSD-free controls (70.2% females)	Grey matter volume analysis	Medial and lateral	Decreased grey matter volume vermis and right hemisphere PTSD patients < controls, correlation between vermis grey matter loss and PTSD symptoms	Baldaçara et al., 2011
PTSD patients and trauma-exposed, PTSD-free controls (70.2% females)	Grey matter volume analysis	Medial and lateral	Decreased grey matter volume vermis and right hemisphere PTSD patients < controls, correlation between vermis and left cerebellum grey matter loss and PTSD symptoms	Baldaçara et al., 2012
PTSD and OCD patients (gender-matched)	Grey matter volume analysis	Posterior lobe, lateral, left hemisphere	Decreased grey matter volume PTSD patients < OCD patients	Cheng et al., 2015
PTSD patients and combat-exposed healthy controls (unspecified gender)	Grey matter volume analysis	Posterior lobe, bilateral	Increased grey matter volume PTSD patients > controls	Sussman et al., 2016
PTSD patients and trauma-exposed controls (57.1% females)	Resting-state SPECT	Posterior lobe, lateral	Decreased functional connectivity early life stress-exposed < controls with the inferior parietal lobule	Bonne et al., 2003
PTSD patients and trauma-exposed controls (unspecified gender)	Resting-state PET	Lateral, various spots	Positive correlation between childhood maltreatment severity and cerebellum-amygdala functional connectivity	Molina et al., 2010
PTSD patients and trauma-exposed controls (32.5% females)	Resting-state fMRI	Posterior lobe, lateral-medial	Increased resting-state activity index PTSD patients > controls	Bing et al., 2013
PTSD patients and trauma-exposed controls (gender-matched)	Resting-state fMRI	Anterior lobe, lateral, right	Increased resting-state activity index PTSD patients > controls	Yin et al., 2011
Remitted and non-remitted PTSD patients (75% females)	Resting state fMRI	Posterior lobe, bilateral	Resting-state activity index differentiates between PTSD patients in remission and those who did not achieve it	Yuan et al., 2018
PTSD patient (male)	Exposure to trauma-related cues, PET	Unspecified	Increased activity upon trauma-related cue exposure that diminishes after SSRI treatment	Fernandez et al., 2001
PTSD patients (unspecified)	Exposure to trauma-related or neutral cues, PET	Anterior lobe, medial	Increased activity trauma-related > neutral cues	Pissiota et al., 2002
PTSD patients (91% females)	Exposure to trauma-related cues, PET	Posterior lobe medial and lateral (left)	Correlation between re-experiencing symptoms and cerebellar activation	Osuch et al., 2001
PTSD patients and trauma-exposed controls (63% females)	Exposure to trauma-related or neutral cues, fMRI	Posterior lobe, lateral (left)	Increased reactivity to trauma-related cues patients > controls	Yang et al., 2004
PTSD patients and trauma-exposed controls (unspecified gender)	Exposure to trauma-related or neutral cues, fMRI	Anterior lobe, medial	Increased reactivity to trauma-related > neutral cues in patients > controls	Ke et al, 2016
Male PTSD patients and war-exposed controls	Exposure to trauma-related or neutral cues, fMRI	Various locations	Increased reactivity to trauma-related > neutral cues in patients > controls reduced after successful mindfulness treatment	Bremner et al, 2017
PTSD patients and healthy controls (54.3% females)	Exposure to subliminal or supraliminal trauma-related or neutral cues, fMRI	Posterior lobe, lateral, right	Increased reactivity to trauma-related > neutral cues in patients > controls	Rabellino et al., 2016
PTSD patients (60% females)	Resting-state functional connectivity MRI	Posterior lobe, bilateral	Reduced functional connectivity between cerebellum and amygdala after neurofeedback training	Nicholson et al., 2017
Dissociative PTSD patients, non-dissociative PTSD patients and controls (74.2% females)	Resting-state functional connectivity MRI	Posterior lobe, lateral, left	Increased functional connectivity between cerebellum and amygdala dissociative PTSD patients > non-dissociative PTSD patients	Nicholson et al., 2015
PTSD patients, trauma-exposed and healthy controls	Resting-state functional connectivity MRI	Posterior lobe, lateral, left	Decreased functional connectivity between cerebellum and dorsal anterior cingulate cortex PTSD patients < healthy controls	Chen et al., 2019
Male combat veterans with differing PTSD scores	Resting-state functional connectivity MRI	Anterior and posterior, bilateral	Decreased functional connectivity between cerebellum and medial prefrontal cortex PTSD patients < healthy controls	Clausen et al., 2017
PTSD patients and healthy controls (41% females)	Resting-state functional connectivity MRI	Posterior lobe, lateral, left	Decreased functional connectivity between cerebellum-medial prefrontal cortex and cerebellum-supramarginal gyrus PTSD patients < healthy controls	Holmes et al., 2018
PTSD patients and healthy controls (32.5% females)	Resting-state functional connectivity MRI	Posterior lobe, lateral, right	Decreased functional connectivity between cerebellum and presupplementary motor area PTSD patients < healthy controls	Zhang et al., 2015

(*continued on next page*)

Table 5 (*continued*)

Experimental subjects	Procedural details	Cerebellar region	Main results	Reference
PTSD patients and trauma-exposed controls (60.5% females)	Resting-state functional connectivity MRI	Posterior lobe, lateral, right	Decreased functional connectivity between cerebellum and vision-related brain areas PTSD patients < healthy controls	Shang et al., 2014
Dissociative PTSD patients, non-dissociative PTSD patients and controls (61.9% females)	Resting-state functional connectivity MRI	Various locations	Increased functional connectivity anterior cerebellum-hippocampus PTSD patients > controls, decreased functional connectivity posterior cerebellum-multiple cortical regions dissociative PTSD patients < healthy controls	Rabellino et al., 2018a
PTSD patients and healthy controls (34% females)	Resting-state functional connectivity MRI	Anterior lobe medial–lateral, left	Increased functional connectivity between cerebellum and periaqueductal grey in PTSD patients > healthy controls	Thome et al., 2017
Dissociative PTSD patients, non-dissociative PTSD patients and controls (65.7% females)	Resting-state functional connectivity MRI	Posterior lobe, lateral, left	Increased functional connectivity between cerebellum and periaqueductal grey in dissociative PTSD patients > non-dissociative PTSD patients	Harricharan et al., 2016
Dissociative PTSD patients, non-dissociative PTSD patients and controls (61.9% females)	Resting-state functional connectivity MRI	Anterior-posterior transition zone, medial and (bi)lateral	Increased functional connectivity between cerebellum and BNST in dissociative PTSD patients > healthy controls	Rabellino et al., 2018b
PTSD patients, trauma-exposed and healthy controls (52.6% females)	Fear conditioning + fMRI	Anterior, lateral, left	Increased response CS+ > CS- in PTSD patients > trauma-exposed controls	Steiger et al., 2015
PTSD patients and trauma-exposed controls (53% females)	Fear conditioning + fMRI	Posterior, lateral-medial, left	Decreased response to CS + during late extinction trials	Rougemont-Bucking et al., 2011
PTSD patients and trauma-exposed controls (69.1% females)	Involuntary memory retrieval task + fMRI	Posterior, lateral-medial, left	Interactive effect PTSD diagnosis-training phase (PTSD patients > controls early, PTSD patients < controls late)	Hall et al., 2018
PTSD patients and trauma-exposed controls (77.8% females)	Loud sound exposure + fMRI	Posterior, lateral, left	Increased loud sound reactivity PTSD patients > controls	Naegeli et al., 2018
Female PTSD patients and trauma-exposed controls	Fearful face exposure + fMRI	Posterior, lateral, right	Increased fearful face reactivity PTSD patients > controls	Stevens et al., 2013
PTSD patients and healthy controls (54.1% females)	Thermal stimuli exposure + fMRI	Posterior, medial and (bi)lateral	Increased heat stimuli reactivity PTSD patients > controls	Elman et al., 2018

compared to war-experienced, psychopathology-devoid soldiers (Molina et al., 2010). Likewise, motor vehicle accident survivors diagnosed with PTSD present increased amplitude of low-frequency activity fluctuations in resting conditions (when compared to controls) in the posterior hemispheres and extending towards medial areas (Bing et al., 2013). Comparing basal brain activity of earthquake survivors with PTSD and trauma-exposed, sex-matched controls with this same method revealed a similar result. However, the activation peak appears in a slightly more anterior zone (Yin et al., 2011). Activity in this same area in resting-state conditions in a sample of men and women diagnosed with PTSD is a predictor of paroxetine therapeutic efficiency (Yuan et al., 2018). These studies provide evidence of functional alterations in the cerebellum of PTSD-suffering individuals, and some of them are good predictors of disease scores and therapeutic option efficiency.

Furthermore, the cerebellum responds to trauma-associated stimuli when they are presented to PTSD patients. An initial assessment of brain glucose metabolism in a man with war-torture-related PTSD showed the cerebellum is significantly active after exposure to war-related sounds. Cerebellar activation decreases after treatment with fluoxetine (Fernandez et al., 2001). Further investigations that monitored brain metabolic activity also report cerebellar increases in different PTSD groups. This phenomenon is true for a study that assessed basal brain activity levels in male war veterans (Pissiota et al., 2002) and a group of 11 women and 1 man with heterogeneous disease-eliciting traumas (Osuch et al., 2001). In the latter study, cerebellar activation upon trauma cue presentation correlates positively with the intensity of the experienced flashbacks.

Adolescents of both sexes who developed PTSD after an earthquake also show significant cerebellar activation when exposed to earthquake-like ground movements and images (Yang et al., 2004). Additionally, mining-accident-PTSD patients exhibit increased cerebellar response to trauma-related cues. Cerebellar activity is significantly reduced at a 2-year follow-up scan, and this activity negatively correlates with PTSD symptom improvement (Ke et al., 2016). Likewise, war-related PTSD male patients display enhanced responsivity to trauma versus neutral cues, which decrease after successful mindfulness treatment (Bremner et al., 2017). These two studies add to others discussed in this section (Baldaçara et al., 2011, 2012; De Bellis et al., 2015; Yuan et al., 2018) to demonstrate a consistent link between cerebellar changes and disease indicators.

Interestingly, an investigation on the subliminal processing of trauma-related words in PTSD patients of both sexes versus sex-matched controls found a zone in the cerebellar hemispheres is significantly activated by subliminal trauma (versus neutral) cues in patients (Rabellino et al., 2016). In this study, the authors propose the cerebellum to be part of an innate alarm system that is strongly coherent with the role for this brain area that will be postulated in the next section.

Another source of evidence provided by neuroimaging studies on the cerebellum-PTSD relationship comes from functional connectivity studies. By using this technique, researchers can describe the temporal relationships of activation patterns of distal brain areas in resting or task-related conditions. Nicholson et al. (2017) examined the effects of a neurofeedback session in functional connectivity patterns of PTSD patients; there is an interaction between training effect and basolateral amygdala-cerebellum functional connectivity reduction. There is also a negative correlation between these connectivity results and the relaxing effects of the neurofeedback session. Intriguingly, connectivity of these same brain areas is apparently enhanced in the dissociative subtype of PTSD (Nicholson et al., 2015).

Connectivity anomalies of the cerebellum with cerebral cortical regions also occur, including decreased connectivity between anterior cerebellar regions and the anterior cingulate cortex (when compared to healthy controls; Chen et al., 2019). Moreover, a resting-state functional connectivity analysis of prefrontal regions of interest shown to

behave differently as a function of PTSD diagnosis in a neuropsychological assessment revealed decreased functional connectivity between the medial prefrontal cortex (mPFC) and anterior and posterior hemispheric cerebellar regions. Correlational analyses demonstrated a negative association between mPFC-cerebellum connectivity and PTSD symptoms (Clausen et al., 2017). Likewise, PTSD patients present decreased intrinsic cerebellar and cerebellum-supramarginal gyrus connectivity when compared to healthy controls (Holmes et al., 2018). The presupplementary motor area also presents decreased synchronous activity with the cerebellum in PTSD patients compared to non-traumatized controls (Zhang et al., 2015). An earlier study that assessed resting-state functional connectivity networks of earthquake victims who developed PTSD demonstrated increased co-occurrence of activation signals with the cerebellum and visual network compared to healthy subjects (Shang et al., 2014). Moreover, a specific cerebellar functional connectivity assessment in PTSD patients who did or did not present substantial dissociative symptoms reported profound alterations that depend on the presence of these symptoms and the studied cerebellar region. When compared to healthy controls, non-dissociative PTSD patients exhibit decreased functional connectivity of the posterior cerebellum with prefrontal cortical regions and enhanced connectivity of anterior cerebellar regions with posterior insula, hippocampus, and visual regions. In contrast, dissociative PTSD patients present decreased connectivity between frontal subregions and the posterior cerebellum (Rabellino et al., 2018a). The PAG, a structure that receives direct amygdalar inputs to initiate fear-related behaviors, also exhibits connectivity alterations with the cerebellum in PTSD. Concretely, anterior cerebellar areas show enhanced synchronous activity with the PAG when compared to healthy controls (Thome et al., 2017). However, when dissociative and non-dissociative PTSD patients are compared, the former group presents enhanced connectivity of the posterior cerebellum with this midbrain structure (Harricharan et al., 2016). The dissociative PTSD subtype also demonstrates enhanced cerebellar connectivity with the bed nucleus of the stria terminalis (Rabellino et al., 2018b). This brain structure is considered to be a part of the extended amygdala and is a crucial mediator of stress-induced responses (Oliveira et al., 2018; Vasconcelos et al., 2019). These studies contribute to the previously reported cerebellum-amygdala connectivity alterations (Gilboa et al., 2004; Dean et al., 2014; Golkar et al., 2014; Nicholson et al., 2015, 2016) and indicate stress-induced deregulation of cerebellar connectivity with areas that mediate responses towards aversive stimuli and the stress response itself.

Aside from these investigations, there are a number of studies that report differential task-related cerebellar activity patterns in PTSD patients when compared to psychopathology-devoid populations. Those reports assessed associative learning, emotional reactivity, or other cognitive abilities in these patients. With respect to associative learning processes, studies showed differential cerebellar participation in fear conditioning paradigms as a function of PTSD diagnosis. Specifically, anterior cerebellar regions are more responsive during contextual fear conditioning acquisition in PTSD patients of both sexes than in PTSD-free, trauma-exposed individuals (Steiger et al., 2015). During fear extinction, however, the results are different, since PTSD is associated with decreased posterior cerebellar activity during the late trials of the extinction session (Rougemont-Bücking et al., 2011). Additional assessments showed an enhanced ability of PTSD-afflicted individuals to retrieve memories with emotional content, accompanied by increased cerebellar activation (Hall et al., 2018). Enhanced cerebellar reactivity in PTSD patients versus psychopathology-devoid individuals occurs when loud sounds (Naegeli et al., 2018), fearful faces (Stevens et al., 2013), or heat stimuli (Elman et al., 2018) are presented, data that suggest cerebellar dysfunction is part of PTSD-associated impairments.

Taken together, these studies provide compelling, multimodal evidence of cerebellar involvement in stress-related neural effects in human beings, including PTSD patients. Nonetheless, within the reviewed studies, explanations on the role of this activation are often lacking or limited to mentioning that the cerebellum appears to be involved in fear/emotion or cognition. Indeed, a specific role for this brain area as having the ability to confirm results from non-human experimental animals and humans has not yet been proposed. Thus, the next section attempts to provide such an explanation.

5. Stress-induced impairment of cerebellar predictive functioning as a contributor to stress-induced behavioral alterations

5.1. Potential confounding factors

Overall, the collected evidence from both human and animal studies indicates that: 1) the cerebellum is heavily connected with a variety of areas that mediate stress-related behavioral alterations, 2) acute and/or repeated stressor application exerts a myriad of effects on cerebellar integrity and function in non-human experimental animals and humans, and 3) PTSD-suffering patients present structural and functional cerebellar alterations that are associated with disease indicators and sensitive to successful treatment interventions. Nevertheless, the possibility remains that several methodological factors could account for the variability found between studies.

In human studies, variables such as the number of subjects, age, sex, years of diagnosis, presence of psychopathologies, and previous treatments are not equivalent among most studies. Differences in the neuroimaging techniques used for monitoring activity, which include PET and functional magnetic resonance imaging (fMRI) scans, and differences within the studies using the same technique (different tracers for PET scans, different intensities of magnetic fields in fMRI studies) could have influenced the results. There are some divergent results in animal studies (Miller et al., 1987; Drugan et al., 1989; Barnhill et al., 1991; Park et al., 1993; Concas et al., 1993; Revilla et al., 1999). These results might be due to the different nature of the stressor, the duration of stressor exposure, and/or the different proportion of studies performed in rats or mice that report those results.

With regards to how representative these results might be from a sex perspective, the human studies normally include men and women in the experimental and control groups. The studies that included only one sex also reported significant differences at the cerebellar level, but there was one report (Seo et al., 2019) that found differential responsivity to stress-inducing stimuli as a function of sex. Nevertheless, the fact that research that included both sexes together or only one of them also showed significant cerebellar differences indicates that the cerebellum is involved in the stress response in men and women. On the other hand, animal studies generally only include males. This factor could be limiting with regards to explaining the obtained results. Nonetheless, some studies assessed the same parameters in male and female rodents. The fact that comparable results are found in both sexes (Corda et al., 1980; Concas et al., 1993; Bitran et al., 1998; Rubin and Ferrendelli, 1997) also supports the general cerebellar involvement in the stress response.

Another concern that might arise is whether the c-fos expression observed in the animal studies is due to differences in locomotion between stressed and non-stressed groups, given that the studies did not include a group with equal locomotion to control for this factor. However, the cerebellar differences observed in neuroimaging animal studies (which tested the animals while anesthetized) make it difficult to assume that c-fos expression is only due to potential locomotion differences. Similarly, stress-induced behavioral effects are reduced by cerebellar stimulation (Bambico et al., 2018), results that make it difficult to ascribe cerebellar changes to locomotion impairments.

5.2. Anticipation/prediction processes and the cerebellum

When examining the functional role of the cerebellum in stress-induced behavioral alterations, the first aspect that indicates potential relevance is the well-described relationship between the cerebellum

and prediction processes.

From a theoretical standpoint, one of the proposed main cerebellar functions is to support generalized, fast prediction processes (Courchesne and Allen, 1997; Wolpert et al., 1998). Such a function is thought to be performed by "forward controllers" (Wolpert et al., 1998; Brown and Brüne, 2012). A forward controller is a brain circuit capable of recruiting forward models to produce anticipatory responses. Forward models, in turn, are internal representations of specific contexts or environments from which an individual is able to estimate the consequences of his/her actions in a given environment (Van der Meer and Redish, 2010). Importantly, the cerebellum is widely considered to act as a forward controller (Miall et al., 1993; Ito, 2008). This idea supposes that, via the use of internal memory and environmental input processing, cerebellar systems can provide a virtual scenario that generates fast prediction of outcomes for a particular behavior (D'Angelo and Casali, 2013). The neural signals that encode this prediction would then be transmitted to effector structures in charge of executing the appropriate behavioral response. In the case of a potentially harmful environment, the transmission of these signals would lead to readiness to execute defensive behaviors. At a neural level, it is conceivable that aberrant functionality of this cerebellum-based predictive system could be indicated by cerebellar activity changes observed after presenting stress-inducing stimuli. It is worth noting, however, that defensive responses might present as behavior-activating (increased arousal and restlessness) or behavior-depressing (avoidance of threatening stimuli or suppression of other naturally occurring behaviors).

Intriguingly, this prediction process is proposed to be performed by the cerebellum in other domains (Adamaszek et al., 2017). Studies in patients afflicted by cerebellar lesions show emotional perception and recognition impairments that are especially pronounced for negative emotions (Annoni et al., 2003; Adamaszek et al., 2014; Lupo et al., 2015). Those findings were previously related to a general predictive function of the cerebellum (Molinari et al., 2008). Furthermore, a meta-analytic work demonstrated that the cerebellum is involved in aversive-learning-related prediction error in human subjects (Garrison et al., 2013).

This hypothesis could also explain the involvement of the cerebellum in associative learning paradigms. Associative learning mechanisms are used by an organism for more efficient adaptation by predicting the appearance of relevant stimuli based on the presentation of previously associated ones that are initially neutral. Therefore, the relationship between prediction/anticipation processes and associative learning is evident. Aversive learning paradigms applied to PTSD patients have indeed provided support for differential cerebellar involvement in these individuals when compared to controls (Rougemont-Bücking et al., 2011; Steiger et al., 2015). Moreover, fear conditioning studies in rodents provide causal evidence on the cerebellum-associative learning link, since cerebellar lesion or inactivation impairs the ability of the subjects to display the classically conditioned anticipatory response (Sacchetti et al., 2002; Koutsikou et al., 2014). Similarly, mice that learn to associate drug administration with the presentation of a cocaine-paired stimulus in a cocaine-conditioned preference paradigm display enhanced GC activation and increased restrictive plasticity mechanisms in the inhibitory interneurons that control GCs (Carbo-Gas et al., 2014, 2017).

Additional evidence that supports a cerebellar role in anticipatory responses also comes from the study of reward-related behaviors. Anticipation of psychostimulant administration in cocaine addicts enhances cerebellar activation, and this effect is unrelated to the pharmacological effects of the administered drug (Volkow et al., 2003). In rodents, cerebellar GCs were imaged while mice performed two different reward-related paradigms that required markedly different motoric requirements to obtain the reward. GCs encode reward anticipation in both paradigms tested (Wagner et al., 2017).

5.3. How might stress impair cerebellum-based predictive functions?

The support provided by the studies mentioned in Section 5.2 about the cerebellar involvement in prediction processes (together with the studies that demonstrate stress-induced cerebellar changes) allow one to hypothesize that subjects exposed to repeated or traumatic stress possess a malfunctioning cerebellum-based predictive system. This maladaptation would promote overestimation of environment-associated harms and concomitantly reduce the perceived success likelihood of potential actions.

This proposed cerebellar role would be consistent with the described behavioral effects of repeated stressor application in non-human experimental animals, namely depression and anxiety-related behaviors. Accordingly, stressed subjects would perceive the typical testing environments for these behaviors as more threatening. Therefore, in assessments of depressive behaviors like the forced swim test, stressed animals spend less time wasting energy trying to escape the water-filled cylinder (Dubey et al., 2015) and seem to resign themselves to stay in those conditions until the environment changes. Likewise, anxiety-assessing environments, including the elevated plus maze or the dark-light test, rely on the conflict that supposes the investigation of a novel, potentially reward-containing environment where the rodent is also more exposed to potential identification by a predator or injury (Salum et al., 2003; Walf and Frye, 2007). In this case, prediction of the novel environment as more threatening than it is by stressed subjects could explain the reduced investigation of the conflict-inducing environment, namely the open arms or the lit zone in the aforementioned anxiety paradigms.

In the case of human beings who suffer from stress-associated psychiatric conditions, the system would work in a similar manner. For example, a patient who suffers from stress-induced depression would likely refuse an offer to join a social event. His/her cerebellum-based predictive system would not be working appropriately, and he/she would predict excessive potential negative outcomes. These outcomes might include being scrutinized, not being able to "fit", et cetera. However, a healthy/resilient person would not anticipate such negative outcomes so prominently, owing to his/her functional cerebellum-based predictive system. As a result, the person could experience potentially beneficial outcomes like having a good time or meeting new people.

In the case of PTSD, a PTSD-free person with or without war experience who encounters another individual with amputated limbs on the streets will likely have an empathy-driven unpleasant emotional reaction. However, this encounter will have little-to-no impact in the behavior of the physically healthy person. His/her cerebellum-based predictive system is functioning correctly, and this fact allows him/her to understand that the particular context in which they met has nothing to do with the other person having lost his/her limb. Therefore, no potential harm is predicted. On the contrary, a war-related PTSD patient (who presents a malfunctioning cerebellum-based predictive system) who is exposed with this same situation would not be able to realize s/he is in a non-war-related context, and would thus interpret it as an extremely threatening situation. This enhanced negative outcome prediction would potentially result in experiencing disease-related symptoms such as physical/emotional distress or the reappearance of trauma-related memories. This assumption is supported by the fact that PTSD patients present enhanced cerebellar activation when they are exposed to trauma-related cues (Fernandez et al., 2001; Osuch et al., 2001; Pissiota et al., 2002; Yang et al., 2004; Ke et al., 2016), owing to their ability of provoking anticipation of harmful outcomes. Additionally, studies on threat anticipation in PTSD patients demonstrate hyper-reactivity to this anticipation and increased distress self-reports (Grillon et al., 2009; Simmons et al., 2013; Duan et al., 2016; Brinkmann et al., 2017). Moreover, anticipation impairments occur in MDD (Forbes et al., 2009; Strigo et al., 2013; Ubl et al., 2015) and anxiety disorders (Andrews et al., 1994; Tillfors et al., 2002; Hazlett-

Stevens and Borkovec, 2004; Grillon et al., 2008), the main psychiatric conditions caused by sustained stress exposure in humans.

At a neurobiological level, upon presentation of an environmental challenge, cerebral cortical input that signals environmental modifications would reach the cerebellum through MFs. MF input would then reach GCs. In line with data reported by Wagner et al. (2017), it is likely that these cells perform computations that are largely responsible for the posterior behavioral response, so the author speculates that such computation could actually reflect the comparison with the cerebellum-based internal model. After GCs integrate environmental-change-related MF signals, information would reach the PCs through the PFs. Then, the differential input provided to PCs would be transmitted to the DCN, which are responsible for delivering cerebellar output to effector structures like the PAG and spinal regions. Upon stressor exposure, this mechanism would function in an aberrant manner and cause GCs to inappropriately integrate the MF input. Ultimately, this dysfunction would result in imbalanced cerebellar output to effector structures. This process would enhance the estimation of negative outcomes and be accompanied by exacerbated defensive reactions, which would be expressed differentially as a function of the patient's disorder or the context. Since the cerebellar organization is strikingly uniform, researchers suggest that it performs a single computational function, and the different domains it affects are dictated by the particular connections of a certain cerebellar region (D'Angelo and Casali, 2013). Accordingly, the cerebellar regions in charge of processing this emotionally relevant environmental challenge might differ from those that provide a similar function for limb control (Ito, 2008). They may receive substantially more input from limbic and perception-related cortical regions rather than pure motor cortical areas. This supposition is supported by the very limited number of human studies that describe functional connectivity changes between the cerebellum and motor cortical areas as a response to or function of stress (Zhang et al., 2015). Furthermore, functional connectivity impairments between the cerebellum and emotion-related brain areas such as the amygdala (Gilboa et al., 2004; Dean et al., 2014; Golkar et al., 2014; Nicholson et al., 2015, 2016), and between the cerebellum and sensory processing areas (Philip et al., 2013; Shang et al., 2014; Holmes et al., 2018; Rabellino et al., 2018a), would support this proposal. The output, however, would likely be directed predominantly to effector structures, but some feedback would be provided to cortical-limbic brain areas. This feedback might help tune the emotional reaction towards a particular stimulus or guide decision-making processes when similar situations are encountered. The consistent finding of connectivity impairments between the cerebellum and the amygdala in stressed individuals supports the idea that emotional valence assessments can be an important part of the cerebellum-based prediction processes impaired by stress. A schematic representation of how the system would work under stressful and non-stressful conditions can be found in Fig. 3.

Furthermore, this proposed cerebellar function is highly compatible with a recent suggestion that considers the cerebellum as a part of an innate alarm system gone awry in PTSD patients (Rabellino et al., 2016; Lanius et al., 2017). These researchers suggest that the cerebellum plays an important homeostatic-like role in this system due to its monosynaptic connections with stress-related midbrain areas, which would be particularly relevant for rapid adaption to potentially challenging environments. This proposal is entirely consistent with an internal model-based prediction process in the cerebellum (as suggested above). In PTSD patients, the aberrant functioning of this cerebellum-based system would increase negative outcome anticipation and delivery of cerebellar output to stress-related and effector structures to trigger anxiety-like reactions characteristic of this disorder.

Overall, taking into account the cerebellar involvement in prediction processes, the abundant effects of stress on cerebellar structure and functioning, and numerous studies that report cerebellar changes in PTSD patients, the proposal of a stress-induced cerebellum-based aberrant prediction process appears to encompass the previously mentioned findings and could underlie the behavioral alterations caused by stress in non-human experimental animals and humans. Support for a causal role of the cerebellum in stress-induced behavioral alterations is provided by a study that shows cerebellar stimulation reduces stress-induced depressive-like behavior (Bambico et al., 2018).

6. Conclusions and future directions

The proposal of a stress-induced cerebellum-based aberrant prediction process is consistent with the aforementioned findings. However, it would need to be tested further, as direct evidence that indicates stress-induced cerebellar activity alterations reflect malfunctioning prediction processes is not available. Similarly, there are a number of experimental approaches that would help reinforce consideration of the cerebellum as a crucial mediator of stress effects.

The previously mentioned study (Bambico et al., 2018) provides support for the use of non-invasive brain-stimulating techniques in stress-induced MDD to target the cerebellum and induce long-term plasticity changes that would reduce symptoms. The abundant neuroimaging findings of cerebellar alterations in PTSD patients support a similar approach in PTSD-affected individuals. To verify that cerebellar activity reflects the functioning of a forward model leading to predictions of upcoming negative outcomes in stressed/PTSD patients, some other approaches could be taken. Presenting patients with ambiguously or mildly threatening cues, or cues that signal a probable but not definitive adverse event, and then measuring their threat-like physiological responses and brain activation would shed light on whether such a cerebellum-supported aberrant harm prediction occurs in these

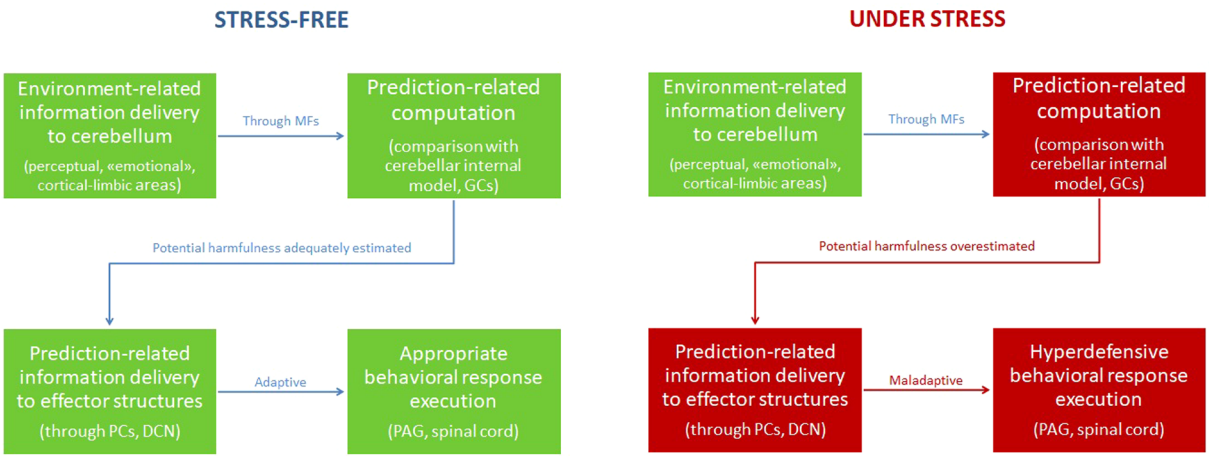

Fig. 3. Representation of the functioning of the cerebellum-based predictive system and its impairment by stress.

patients. Subsequently, the effect of non-invasive cerebellar stimulation on patients' estimations of negative outcomes after cue presentation could also be assessed. This approach could provide therapeutic benefit if proven successful.

In rodent studies, presenting stressed and non-stressed subjects with ambiguous cues and evaluating whether they anticipate any harm (Enkel et al., 2010) associated with potential cerebellar changes would reinforce cerebellar involvement in stress-induced increased threat anticipation. Causal evidence could be provided by attempting to reverse this adverse event anticipation via cerebellar activity modifications. Techniques like optogenetics or designer receptors exclusively activated by designer drugs (DREADDs) could be used in rodents to specifically manipulate a cell subtype or a particular pathway that connects the cerebellum to stress-related brain areas. Interesting targets for this manipulation, which present monosynaptic connections with the cerebellum, would include midbrain areas like the PAG (Koutsikou et al., 2014), locus coeruleus (Schwarz et al., 2015), and/or VTA (Carta et al., 2019).

Additional preclinical experimental approaches with increased potential to be translated to clinical settings might also study the relationship between environmental enrichment (EE) and stress-induced cerebellar changes. This possibility is appealing because EE ameliorates stress-induced behavioral alterations (Novaes et al., 2017; Seong et al., 2018), and it also induces neuroplastic-like changes in the cerebellum (Vazquez-Sanroman et al., 2013). Therefore, further investigation about this relationship might provide neurobiological validation of therapeutic strategies analogous to EE for PTSD patients.

Another interesting option would be pharmacologically targeting a specific component of the neurotransmitter systems altered in the cerebellum as a response to stress. Unfortunately, the receptors and subunits expressed in the cerebellum and the rest of the brain are essentially the same, but this situation is not the case for the alpha6 subunit of the $GABA_A$ receptor. This protein is exclusively expressed in the cerebellum (Galliano et al., 2013; Carbo-Gas et al., 2017), and it thus represents a target that could assist in stress-induced symptoms and disorders. Given that no pharmacological compound that specifically targets this subunit is available on the market, it represents an interesting research line for companies or laboratories interested in stress neuropharmacology.

In conclusion, stress-related behavioral impairments and disorders can become severely debilitating conditions that lack fully effective treatments, possibly influenced by incomplete understanding of its neurobiological basis. Cerebellar changes occur after stressful experiences in non-human experimental animals and humans, including patients. Furthermore, the cerebellum is strongly linked with predictive processes, and enhanced threat anticipation also occurs in patients who suffer from stress-related disorders. Therefore, it is possible the cerebellar changes that occur in response to stress reflect aberrant prediction processes. As a result, the chances of obtaining a negative outcome from an environmental challenge are overestimated. Information regarding this prediction would then be transmitted to other structures, and this process would promote maladaptive responses. Characterizing this process in depth, and performing some of the suggested experiments, would also be helpful in order to develop strategies to normalize aberrant threat predictions. This endeavor, in turn, may lead to a new therapeutic option to reduce stress-induced behavioral alterations and disorders.

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Declaration of Competing Interest

The author declares no conflict of interest.

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