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Focusing on the Possible Role of the Cerebellum in Anxiety Disorders

Meghan D. Caulfield and Richard J. Servatius

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<http://dx.doi.org/10.5772/52954>

1. Introduction

The cerebellum is traditionally thought of as the neural structure responsible for motor control, voluntary movement, balance and associative learning. However, there is a growing awareness that the cerebellum plays a role in higher cognitive functions such as sensory processing [1,2], attention [3,4], verbal working memory [5-8] and emotion [9-11]. Converging evidence suggests that the cerebellum may play a role in anxiety disorders. With the greater appreciation that anxiety disorders are best conceptualized by diathesis models of risk, cerebellar activation may represent an endophenotype contributing to anxiety etiology.

This chapter will present the role of a normal functioning cerebellum and outline instances in which abnormal functioning underlies a variety of pathologies including anxiety disorders. We will begin by describing historically accepted roles of the cerebellum in motor control, timing, and learning and memory. We will then present research relating to less appreciated roles such as executive processing and emotional control to demonstrate less recognized cognitive and emotional capacities of the cerebellum.

Key to our theory is that individual differences in cerebellar activity underlie vulnerability to develop anxiety disorders. This argument will be presented by providing an overview of pre-existing vulnerabilities contributing to a diathesis approach of anxiety. We will discuss recent research in which individual differences in cerebellar modulated activities is present, such as during associative learning, avoidance or image processing tasks. Finally, a diathesis model which incorporates cerebellar activation into the etiology and expression of anxiety disorders will be presented with a discussion of its implications and future directions.

2. Historically accepted roles of the cerebellum

The cerebellum is a unique neural structure that accounts for approximately 10% of the total brain volume and contains nearly half of all the neurons of the brain [12,13]. The cerebellum is highly organized, with distinct inputs and outputs. It is made up of an outer region of gray matter (the cerebellar cortex), an inner region of white matter, and three pairs of deep nuclei responsible for cerebellar output; the dentate, the fastigial, and the interposed [13]. The cerebellum is made up of two hemispheres that are structural mirror images, each containing three deep nuclei. The two hemispheres are connected medially by the vermis. For specificity, the cerebellum is segregated into sections: Crus I, Crus II, and lobules I-X ([14].

Motor Functioning. The traditional view of the cerebellum is that of a motor comparator. Muscle movement, especially coordinated and smooth motions, are the product of a feedback loop involving the cerebellum and frontal cortex. Afferent connections via the cortico-pontine-cerebellar tract with the premotor and motor cortex carry a “copy” of motor demands to the cerebellum. The cerebellum then compares feedback from the muscle spindles, joints, and tendons via the cerebellar peduncles to modify motor behavior, maintain coordination and perform skilled movements [15-17].

The essential role of the cerebellum in motor behavior is especially evident following cerebellar insult. Unlike lesions of the motor cortex, a cerebellar lesion does not eliminate movement entirely. Instead, it disrupts initiation, coordination, and timing of movements. Movement deficits following cerebellar lesions can be very precise. Some lesions affect certain muscle groups, but not others, depending on the location, revealing a precise topography in the cerebellum. For example, deterioration of the anterior cerebellum affects the lower limbs, causing a wide staggering gait, while largely sparing arm and hand movements [18-21]. Cerebellar lesions often lead to a lack of coordination, affecting the ability to perform directed movements. Damage to the vestibulocerebellum, which receives input from the vestibular nuclei, affects gross movements, such as standing upright, to fine movements, such as maintaining fixation of gaze. Spinocerebellar lesions disrupt signals from the spinal cord and affect coordination interfering with movement regulation. The spinocerebellum uses a feed-forward process to make on-line updates to ensure accurate coordinated movements. Lesions of the cerebellum cause a variety of movement disorders such as overshooting or undershooting of targets (referred to as dysmetria), poor path correction caused by poorly coordinated joint motions (known as ataxia), tremors at the end of actions [13,18,22]. Finally, insult of the cerebrocerebellum, which has afferents from the cerebral cortex, impairs planned movements and sensory input, affecting reaction time. Individuals with lesions to the cerebrocerebellum report difficulty performing directed actions. Instead of a smooth integration of movements toward a target, their actions take place as a series of several movements strung together, known as decomposition of movement [18]. Altogether, the profound and specific outcomes of cerebellar insult indicate its critical role in coordinated motor behavior, enabling smooth and accurate performance of highly specific fine motor movements.

Timing. Given its role in motor behaviors outlined above, it is not surprising that the cerebellum is essential in motor timing, which produces timed movements by coordinating velocity, acceleration and deceleration [15,23-28]. A simple way of measuring motor timing is through repetitive finger tapping tasks. Participants are asked to tap in time with a pacing device (e.g., metronome). After synchronization, the training device is removed and the individual is asked to continue tapping at the same interval. Variability in timing can then be measured in the inter-tap intervals. This simple task elucidates the essential role of the cerebellum in motor timing. Healthy participants demonstrate a significant increase in cerebellar activity (in addition to other areas related to motor timing such as the supplementary motor area and basal ganglia) during timed finger tapping [28]. Patients with lateral cerebellar lesions demonstrate increased variability when performing rhythmic tapping with the affected (ipsilateral) finger, but not when tapping with the unaffected (contralateral) finger. Interestingly, those with medial cerebellar lesions did not show timing errors, but had a greater number of motor errors, supporting involvement of the cerebellum specifically in timing and not just in producing the behavioral motor output [23].

Timing is also essential in higher cognitive functions such as stimulus processing, expectations, language, and attention. Sensory timing is often measured by duration judgment tasks, which presents two stimuli of either the same or different duration. Here, participants are required to attend to a stimulus, maintain it in working memory, compare it to a second stimulus and make a judgment. Significant increases in cerebellar activity are present during timing tasks in healthy human participants [29,30]. Additionally, the use of repetitive transcranial magnetic stimulation (rTMS), which induces inhibition and causes a “temporary lesion” in the stimulated region, of the lateral cerebellum impaired short interval time perception in a similar task (400-600 ms) [31]. Comparable sensory timing deficits are seen in children with Ataxia Telangiectasia, a disease involving cortical degeneration affecting Purkinje and granular cell layers [32]. A similar deficit in duration judgment is seen in patients with cerebellar tumors [33]. Furthermore, the effect of cerebellar lesions on sensory timing is not specific to duration judgment tasks. Patients with cerebellar lesions display deficits in a variety of other tasks requiring sensory processing including interval discrimination [24,34], speed judgments [35,36] and verbal timing [37-41].

Eyeblink conditioning. Although the cerebellum has long been acknowledged as a motor integrator and modulator, associative learning was assumed to be accomplished by higher cortical regions. Over the latter quarter of the 20th century, Thompson and colleagues presented a body of work that the cerebellum is part of the intrinsic circuitry for eyeblink conditioning, a form of new motor learning [42-45]. The foundation of eyeblink conditioning is the simple reflex pathway; the unconditional stimulus (US) produces an unconditional response (UR). Introduction of a second stimulus (conditioned stimulus or CS) that is temporally paired with the US gives rise to a conditioned response (CR), which precedes or significantly modifies the UR. In delay conditioning, the CS precedes and coterminates with the US. Thompson recognized that the simplicity of eyeblink conditioning coupled with the ability to explicitly assess reactivity to the CS, to the US, or its combination under various

conditions provided an excellent platform to understand the nature of the engram – the storage and location of a memory trace [42,46,47].

The intrinsic cerebellar circuitry demonstrates why damage to the cerebellar cortex, cerebellar nuclei, or major afferent pathways abolishes or impairs acquisition of the CR during eyeblink conditioning [48-53]. Using rats and rabbits, the neurobiology of eyeblink conditioning has been reduced to two pathways that converge in the cerebellum (For detailed reviews see [45,54]). The basic essential pathway is presented in Figure 1. Simplified, the CS pathway transmits auditory, visual, and somatosensory information via the pontine nuclei to the cerebellar cortex and interpositus nucleus via mossy fiber connections. The US pathway takes two routes from the trigeminal nucleus: a reflexive route that bypasses the cerebellum and a learning route that integrates the relationship between the CS and US. From there, climbing fibers synapse at the cerebellar cortex and interpositus nucleus. The CS and US pathways converge in the cerebellar cortex and anterior interpositus. It is here where the memory trace is stored by changes in the firing patterns of purkinje cells during the development of the CR [47,55-57]. The CR is produced by release of inhibition of the interpositus, which increases activity to the red nucleus, in turn causing the cranial motor nuclei to induce an eye blink response [58,59].

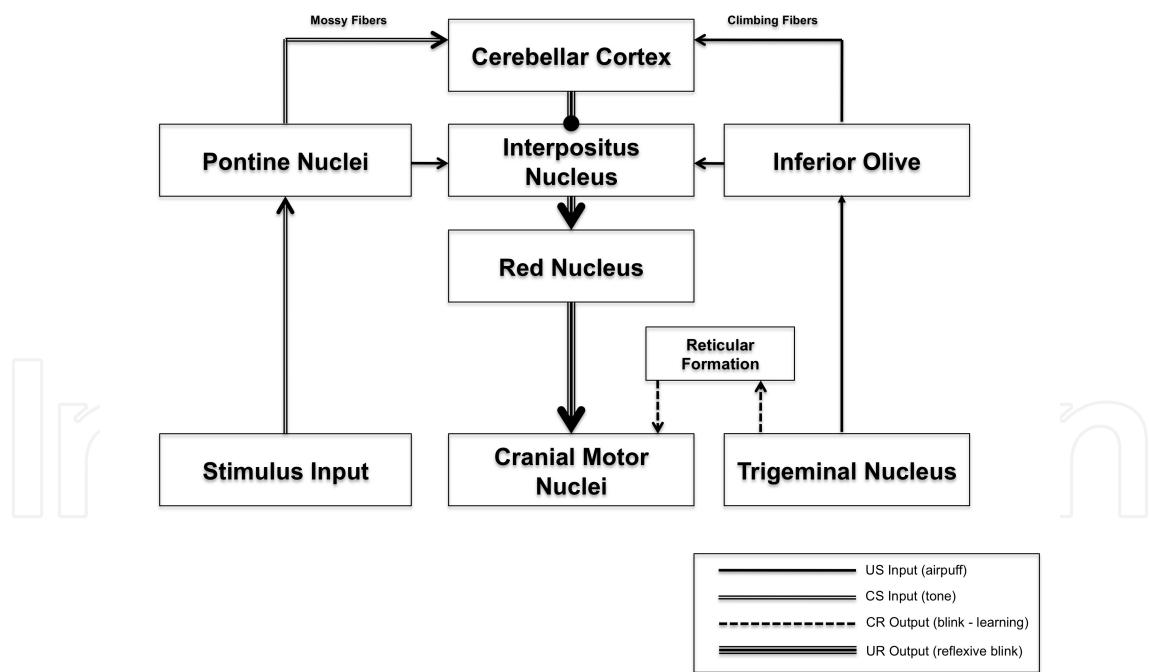


Figure 1. Intrinsic delay eyeblink conditioning pathway. Adapted from Christian & Thompson, 2003.

Another benefit of the eyeblink conditioning paradigm is that the same parameters can be used across animal species, in humans, and even in early infancy. Consistent with the animal literature, intact cerebellar structures are necessary for the acquisition of the CR in eye-

blink conditioning in humans [48-50,60]. Furthermore, imaging studies indicate that activity in the cerebellum is significantly greater during eyeblink conditioning in humans [61-65].

Given the advanced understanding of neurosubstrates and its amenability for cross species comparisons, eyeblink conditioning has been a platform for understanding clinical abnormalities and cerebellar dysfunction. Therefore, a more detailed review will be presented for eyeblink conditioning, as well as a selection of clinical examples in which a cerebellar role is revealed by eyeblink conditioning.

Cerebellar abnormalities and eyeblink conditioning. The cerebellum is particularly affected by ethanol alcohol, with alcohol-related diseases causing serious damage to its development and cells. For example, impaired delay eyeblink conditioning has been observed in Korsakoff patients, recovered alcoholics, and children with Fetal Alcohol Syndrome [66-69]. However, not all disorders cause deficits in eyeblink conditioning. For example, individuals with autism acquire eyeblink conditioning faster than matched controls, although the form of the CR is altered [70,71]. Schizophrenia also alters cerebellar functioning, with facilitated eyeblink conditioning observed in schizophrenics compared to healthy controls [72]. Some interventions can also rescue or improve cerebellar functioning. For example, improved performance in eyeblink conditioning has been observed in mice following an antioxidant rich diet over a standard diet [73].

Regardless of etiology, cerebellar abnormalities affect eyeblink conditioning. The well-documented pathways, substrates, and lesion studies makes eyeblink conditioning a simple, yet sensitive tool to understand the cerebellar role in various neuropathologies.

3. Higher cognitive and emotional capacities

Recently, the cerebellum has garnered greater attention for its higher cognitive capabilities. Reviews such as those from Courchesne and colleagues [3,74], Schmahmann and colleagues [75,76] and others [77-79] establish the cognitive role of the cerebellum, which will be briefly summarized here.

Anatomy. In order to have a role in higher cognitive processing the cerebellum must maintain connections with neural structures known to influence cognition. As such, cerebellar efferents have been traced to both motor and non-motor areas of the frontal cortex [80-85]. Tract-tracing studies with primates indicate that cerebellar output to the dorsolateral prefrontal cortex (DLPFC) places it in a position to modulate higher cognitive processing. Transneuronal retrograde virus tracers injected into multiple areas of the DLPFC (Brodmann areas 9, 46 and 12) labeled neurons in the dentate nucleus, indicating that the dentate has output channels to prefrontal regions [84]. The DLPFC plays an important role in many aspects of executive functioning including organization [86,87], behavioral control [87] working memory [88,89], reasoning and decision making [90], reward and expectancy [91], and emotion and motivation [92]. Follow up studies were able to pinpoint lateral dentate projections to the prefrontal cortex (PFC), with separate dorsal dentate projections terminat-

ing in the motor and premotor regions, suggesting a topographic organization of the dentate nucleus with both motor and non-motor output to the cortex [93].

Functional connectivity. Cerebellar connectivity to non-motor cognitive areas in human imaging research reflects pathways implicated in primate studies. Functional connectivity MRI correlates signal fluctuations in one brain area with activity in another, implying a relationship between the two areas. Using this method, Allen et al. [94] found that activity in the dentate nucleus of the cerebellum correlated with changes in activity in non-motor regions such as the limbic system, parietal lobes, and prefrontal cortex. Connectivity between the cerebellum and anterior cingulate cortex, a region typically associated with error detection, anticipation, attention, and emotional responses, has also been reported in resting state paradigms [95]. Furthermore, there is evidence that the cerebellum contributes to the intrinsic connectivity networks, a series of brain structures that correspond to basic functions such as vision, audition, language, episodic memory, executive functioning, and salience detection [11]. Distinct contributions of the neocerebellum to the default mode network, the executive network, and the salience network substantiate the assertion that there is functional connectivity between the cerebellum and non-motor cognitive regions.

Clinical support for a cerebellar role in non-motor cognitive processes is established by the work of Schmahmann and colleagues. Schmahmann recognized that not all patients with cerebellar strokes present with motor deficits. By assessing motor impairments alongside stroke location, he found that individuals with posterior lobe lesions presented with minor if at any motor impairments. Instead, they suffered from behavioral changes affecting executive functioning, verbal fluency, working memory, abstract reasoning, spatial memory, personality, and language deficits; recently coined as *cerebellar cognitive affective syndrome* [96,97].

Loss of function in lesions is supported by activation studies in healthy humans. Using functional MRI, significant changes in cerebellar activity is present during tasks that are considered largely cognitive or to involve executive processing. Significant increases in cerebellar activity have been recorded during sensory timing [29,30], spatial attention [98-101], and verbal working memory tasks [5,6,102].

Anatomical and functional connectivity, specific activation during executive processing tasks, and impairments concomitant with lesions is convincing evidence that the cerebellum plays a critical role in higher cognitive processing.

Emotions. In addition to connections with prefrontal and frontal cortex, the cerebellum also has direct anatomical connections to the amygdala, the brain region typically associated with emotion and fear [103]. Functional support for this connectivity comes from imaging studies that demonstrate judging emotional intonation, feeling empathy, experiencing sadness, and viewing emotional pictures all correlate with increased activity in the cerebellum [9,76,104-106].

If the cerebellum has important connections to the limbic system, then it follows that stimulation of the cerebellum should result in changes of emotional behaviors. As such, electrical stimulation of the cerebellum in animals demonstrates that it is an important modulator of

behaviors classically attributed to limbic functioning including grooming, eating, and sham rage [107-109]. Bernston et al. [107] reported that stimulating the cerebellum of cats induced grooming and eating behaviors, in addition to similar findings with rats [108,109]. The cerebellum, specifically the vermis, plays a role in fear and avoidant behaviors. For example, lesioning the vermis alters fear responses by decreasing freezing and increasing open field exploration [110]. On the other hand, stimulating the vermis induces fear responses, such as increased amplitude of the acoustic startle response [111], indicating cerebellar modulation of species-specific behaviors beyond coordination of muscle movements.

Reports from the clinical literature also support cerebellar modulation of emotion. Attempts to treat severe seizure disorders by stimulating the cerebellum provide unique case reports of observations about cerebellar functioning. Heath et al. [112] placed electrodes in the fastigial nucleus of an emotionally disturbed patient and observed increased activity in the region when the patient reported being angry or fearful. Descriptions of unpleasant sensations and the feeling of being scared were reported following stimulation of the dentate nucleus [113]. In a larger study of cerebellar stimulation as a treatment for chronic epilepsy, Cooper et al. [114] reported marked behavioral changes from sullen mood, dangerous, and aggressive behaviors to open, pleasant, responsive, and sociable affect in patients. More recently, descriptions of highly specific lesions to the cerebellar vermis includes personality changes, especially emotional effects such as flattening of affect [97,115]. Observations from these case studies suggest that the cerebellum may utilize its reciprocal connections with the prefrontal cortex and limbic system to modulate emotional processing.

Cerebellum and Anxiety Disorders

Anxiety. Anxiety is the most prevalent disorder in the United States with one quarter of the population estimated to develop an anxiety disorder at some time in their lives [116,117]. On the other hand, three quarters of the population does not suffer from clinical anxiety, raising the question what is it about an individual that makes them more likely to develop an anxiety disorder? Unfortunately, there is no single vulnerability increasing risk for anxiety. Instead, anxiety disorders are best represented by diathesis models, that is, preexisting conditions enhance risk such that individuals are vulnerable to environmental insults or challenges. A stress-diathesis model for anxiety disorders emphasizes changes in stress reactivity from the convergence of a variety of factors such as genetics, biology, sex, and prior experience [118]. Current research efforts heavily focus on the higher cortical areas (e.g., prefrontal cortex, cingulate cortex, hippocampus, amygdala) as areas critical to development of anxiety. However, the cerebellum is also intimately involved in emotional processing, learning and memory – all of which are represented as risk factors in diathesis models. The following sections will describe how cerebellar activity is related to the signs and symptoms of anxiety and provide often overlooked evidence of cerebellar involvement from imaging research. This will form the basis for speculations regarding individual differences in cerebellar activity as a risk factor for anxiety disorders.

Avoidance. Avoidance is the core feature in the otherwise varied symptomology of anxiety disorders [119]. Therefore, it is essential to understand the role abnormal expressions of avoidance plays in the development and maintenance of anxiety. First, avoidance is ac-

quired and reinforced over time. The essence of anxiety is concern over a potential threatening event in the future, typically one which the individual feels they have no control over and could not cope with. Rather than deal with uncontrollable events, anxious individuals choose to exert their control by substituting other negative thoughts or feelings that are avoidable, providing short term relief and a feeling of temporary control. Avoidance can either be active or passive. In active avoidance, the individual learns to control their environment by alleviating or removing a noxious stimulus. In passive avoidance, the individual learns not to place themselves in a situation that previously contained a noxious stimulus. In anxiety, both forms of avoidance are present, and over time, become pervasive and uncontrollable such that normal functioning becomes impossible.

Avoidance is a learned process. Therefore, it is possible to measure the differences in acquisition of the negative reinforcement learning seen in active-avoidance. Differences in the speed and strength of acquisition in active-avoidance may contribute to risk or resiliency. Some individuals may be more susceptible to acquire and repeatedly express active-avoidance behaviors, leading to development of behavioral and cognitive avoidance symptoms associated with anxiety disorders.

Although the cerebellum is typically associated with associative learning using classical conditioning protocols, a cerebellar role in operant learning such as avoidance has also been suggested. For example, lever press avoidance paradigms places a rat in an operant chamber and presents a stimulus (e.g., tone) that precedes and overlaps with an aversive stimulus (e.g., a shock). Over time, the rat learns to make a lever press response to the tone, avoiding the shock. Lesioning the cerebellum prevents acquisition of the avoidance response in this task [120] and in other measures of active-avoidance [121]. Furthermore, cerebellar involvement may play a role in human avoidance as well [122].

Neuropharmacology. Given the role of the cerebellum and associative learning in anxiety vulnerability, it would be useful to consider treatment approaches that target the cerebellum. Among others, the cerebellum maintains a large density of corticotrophin-releasing hormone (CRH) receptors and cannabinoid receptors. Here, we will outline how these receptors relate to anxiety and eyeblink conditioning.

The influence of CRH on various behavioral markers of anxiety demonstrates its role in modulating stress reactivity. CRH has anxiogenic properties, with a dysregulation of CRH systems playing a role in anxiety disorders. The cerebellum contains a high density of CRH1 receptors, the receptor linked to stress responding, anxious behavior and cognitive functioning [123]. The effects of CRH receptor activation have been thoroughly outlined using animal models, including its influence on anxiety (for a review see [124]). For example, an injection of corticotropin releasing factor (CRF), which induces corticosterone release (the animal analog of cortisol), has been shown to decrease open field exploration, time spent in open arms in the elevated plus maze, exploration in novel environments, and social interaction in rats at certain doses. Furthermore, injections of CRF increase startle amplitude, and improve acquisition in both active and passive avoidance paradigms. Additionally, CRH receptors are adaptive to environmental demands, with a variety of stressors upregulating CRH1 receptors specifically, suggesting a relationship to chronic stress that may feed for-

ward into anxiety disorders [125,126]. Eyeblink conditioning is also influenced by CRH, with studies demonstrating facilitated acquisition in trace paradigms of both humans and rats [127-129]. Humans treated with metyrapone, which decreases initial cortisol response to stress (although not long term effects of stress [130], acquired trace eyeblink conditioning faster than placebo treated controls. While there were no acquisition differences between the groups in delay-type conditioning, metyrapone treated individuals were significantly slower to extinguish, a difference not seen in the trace group [128]. Altogether, it appears that stress reactivity in the brain impacts cerebellar functioning and may play a role in modulating learning and memory, feeding into anxious behavior and increased vulnerability to anxiety disorders.

Cannabinoid receptors, which have their highest densities in the frontal cortex and cerebellum, have also been linked to anxiety [131-133]. Low doses of cannabinoid compounds induce anxiolytic effects, with high doses causing anxiety-like reactions in laboratory rats, suggesting interplay between cannabinoid receptor activity and anxiety [134-136]. These findings are in conjunction with subjective reports that exposure to cannabis derivatives can induce feelings of placid relaxation or panic [137]. For example, low doses of a cannabinoid synthetic reduces behaviors linked to stress in rats with high doses of the same drug causing the opposite pattern, inducing anxiety to novelty and increasing corticosterone [135]. Aside from synthetic activation, endogenous cannabinoid receptor activity is related to anxiety as well. Pharmacological blockage of the CB1 cannabinoid receptor increased anxiety-like behaviors in rats including reduced open arm exploration in the elevated plus maze and increased withdrawal-related behaviors [132]. Cannabinoids influence anxiety and have a high density of receptors in the cerebellum, suggesting that cannabinoid receptor activation would influence eyeblink conditioning as well. As such, animal models have demonstrated that CB1 knockout mice demonstrate disrupted eyeblink conditioning [138]. In conjunction, humans who report chronic cannabis use (but not at the time of the study) exhibit fewer and poorly timed CRs during delay eyeblink conditioning compared to non-users [139].

Temperament differences contributes to anxiety vulnerability

Diathesis models suggest that the interplay between risk factors increases vulnerability to develop anxiety disorders. Personality is among the many risk factors suggested to play a role in anxiety, with certain personality types at increased risk to develop anxiety disorders. Support for a personality risk factor in anxiety is supported by the low success rates in treating anxiety disorders, which would require the alteration of stable character traits. Of the few studies that have assessed long-term treatment outcomes of anxiety disorders, 30%-50% still have moderate to severe anxiety six years post treatment [140,141].

An understanding of how personality interacts with anxiety is essential. Here, we will discuss an innate feature of personality known as temperament. Temperament is a core feature of personality, often evident early in childhood and remains stable throughout the lifespan. By measuring temperaments related to anxiety such as behavioral inhibition (BI) and trait anxiety, we are able to differentiate at-risk individuals and assess individual differences on cerebellar modulated tasks.

Behavioral inhibition. Similar to anxiety disorders, a core feature of behavioral inhibition is avoidance. Additionally, the behavioral and physiological functioning of an individual with behavioral inhibition is comparable to that seen in anxiety including withdrawal, apprehension, and slow latency to approach unfamiliar people or objects [142]. Kagan and colleagues have provided an extensive behavioral profile of BI using longitudinal methods, reporting that children classified as inhibited at 21-months demonstrate avoidance of social interactions [143], reported more phobias, and had a higher incidence of anxiety disorders [144-147]. As with anxiety disorders, it appears that inhibited temperament is a heritable trait [148]. Parents and siblings of those children classified as inhibited were more likely to have anxiety disorders, social phobia, avoidant and overanxious disorders compared to the families of uninhibited children [149-151].

So far, we have provided evidence supporting that cerebellar differences underlie higher cognitive processes including anxiety disorders. We have outlined the essential role avoidance has in the development and maintenance of anxiety disorders and how learning processes may underlie increased avoidance. We then introduced behaviorally inhibited temperament, a risk factor with many similarities to anxiety. In the next section we will combine individual differences in cerebellar functioning, avoidance, learning, and temperament to provide a cerebellar diathesis theory of anxiety vulnerability.

As described above, avoidance in the development of anxiety disorders is a feed-forward process, such that the expression of avoidance reduces stress in the present while simultaneously increasing the aversiveness of the undesired stimulus or state in the future, increasing the likelihood of continued avoidance behaviors. Both adaptive and pathological avoidance can be described in terms of the degree and rigidity of expression, the sensitivity to acquire stimulus to stimulus associations, and inflexibility to change. Multiple processes underlie avoidance acquisition, making it difficult to tease out the essential factors in anxiety. It is possible that increased sensitivity to the cues and contingencies in the environment are learned faster in anxiety, resulting in better performance on avoidance tasks. One way to measure these associations is through the classically conditioned eyeblink response. The use of eyeblink conditioning allows multiple measures to be taken into account including reactivity, acquisition of the relationship between the CS and US, and rate of extinction.

Learning. The inbred Wistar-Kyoto rat (WKY) provides a model of inherent anxiousness and vulnerability to stress, similar to what is seen in a behaviorally inhibited personality profile [152-160]. Furthermore, the WKY demonstrates enhanced active avoidance in lever-press paradigms, reinforcing the relationship between anxiety vulnerability and avoidance [161,162]. Comparisons of WKY male rats to outbred Sprague-Dawley male rats demonstrate significantly faster acquisition and greater asymptotic performance of the WKY [163,164]. Moreover, avoidance perseverates in WKY during extinction training in the presence of safety signals [159] or avoidance acquisition with more intense stressors [165]. As reviewed by Jiao [166], the WKY provides an animal model of inhibited temperament, faster associative learning, enhanced sensitivity to acquire avoidance, and resistance to extinction. Moreover, the reactivity increases in the face of avoidance acquisition, reminiscent of increased reactivity in PTSD [167].

Striking parallels are evident between rat models of anxiety vulnerable temperament and humans with self-reported inhibited temperament, suggesting a common neural substrate. One way to assess at-risk temperament is through self-report scales such as those that measure behavioral inhibition [168,169] or trait anxiety [170]. Using these measures, our lab has found that at-risk individuals acquire the relationship between the CS and US the faster, demonstrating more CRs earlier in the training period than those who are low scoring [171,172]. For example, a recent study with a large sample of 117 healthy college-age students found that those scoring high on the Adult Measure of Behavioural Inhibition [169] and Trait Anxiety [170] acquired standard delay eyeblink conditioning faster than those who scored below the median on these measures (see Figure 2). Considering the intimate relationship between associative learning of cues as predictors of aversive events, enhanced classical conditioning may reflect increased sensitivity to acquire avoidance responses.

These and other similar results [171,173,174] suggest that individual differences in acquisition of learning tasks may reflect processes underlying increased risk for anxiety disorders.

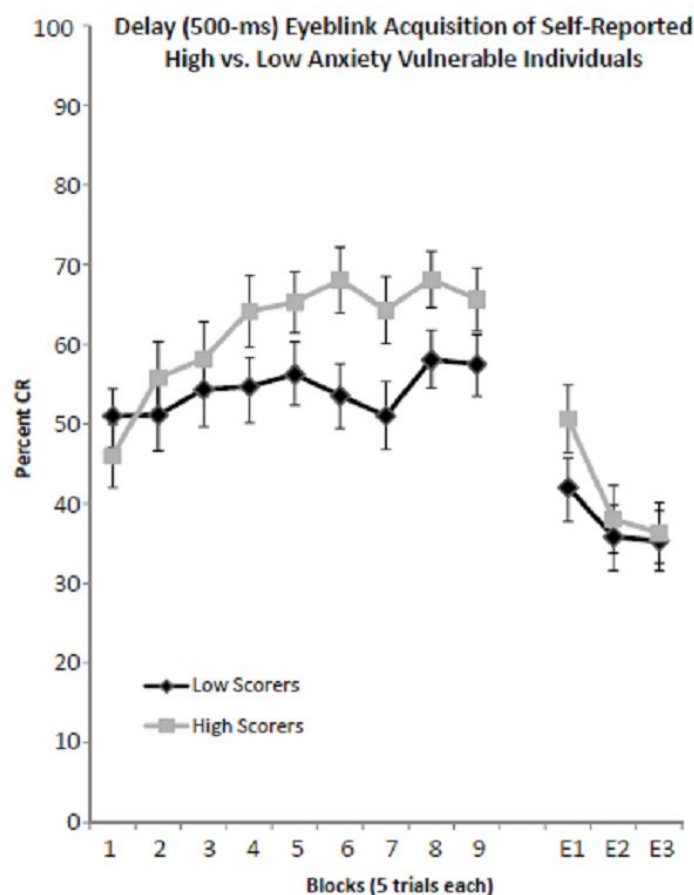


Figure 2. A comparison of temperament on delay eyeblink acquisition of healthy college-aged students. Those who score above the median on the AMBI and STAI-Trait are considered high scorers, those below are considered low scorers. Anxiety vulnerable individuals acquired eyeblink conditioning faster and to a greater degree over the 45 trial training period (blocks 1-9). There were no observed differences in extinction (E1-E3).

Heart Rate. In addition to higher cortical pathways, the cerebellum also has direct reciprocal connections to the hypothalamus. Studies in rats and primates show projections from the deep cerebellar nuclei to the lateral hypothalamus, posterior hypothalamic area, dorsal hypothalamic area, the paraventricular nucleus, and the dorsomedial hypothalamic nucleus (For a review see [175]), some of which may be related to heart rate reactivity.

Research in behaviorally inhibited children indicate that a high and stable heart rate (compared to uninhibited children) is indicative of long-term inhibited temperament. Reduced resting heart rate variability has been revealed as a feature of perceived stress [176] and anxiety disorders such as PTSD [177]. The presentation of novel or negative stimuli in healthy populations results in large bradycardic response, with greater bradycardia to more negatively valenced images [178,179]. While there appears to be a relationship between heart rate and anxiety, few studies have looked at heart rate reactivity in behaviorally inhibited adults. Studies that manipulate heart rate typically do so with negatively valenced pictures, assessing reactivity to extreme stimuli (i.e., trauma images for a PTSD patient). In order to disentangle individual reactivity from heart rate changes during high-arousal image processing, which can cause large responses in everyone, a recent study from our lab assessed heart rate change in high and low BI individuals when viewing images that were low in arousal across positive negative and neutral valence. Using this design, we could better understand how BI influences reactivity to everyday stimuli normally encountered in the environment to see if inhibition is related to aberrant parasympathetic or sympathetic activation. Recordings of 6 seconds before, 6 seconds during, and 6 seconds after image presentation suggest a sustained bradycardia in inhibited individuals compared to their non-inhibited counterparts. It is possible that greater vagal tone in high BI could also be related to the enhanced eyeblink acquisition seen in behaviorally inhibited individuals in across studies in Veterans, high school aged students, as well as college aged individuals (See Figure 3).

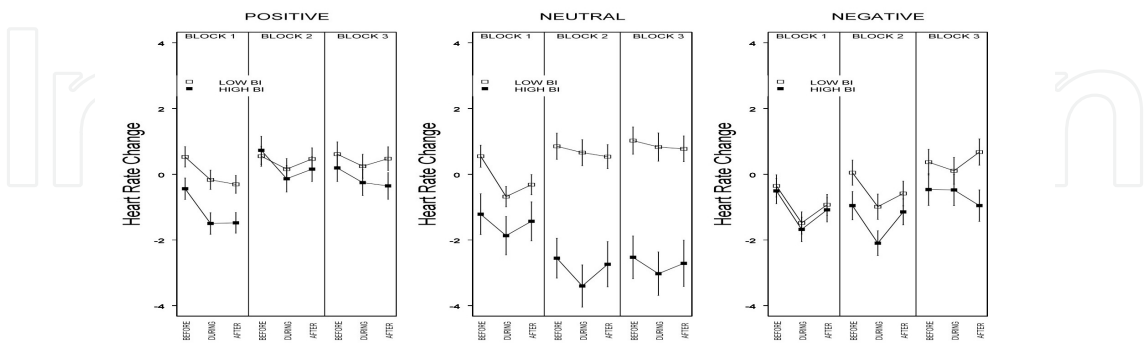


Figure 3. Heart rate change from baseline for positive, neutral, and negative images in high and low behavioral inhibition. Each block represents 20 trials. Behaviorally inhibited individuals showed sustained bradycardia over the neutral picture viewing session. Bradycardia lasted only through the first block of 20 trials in the positive condition, and appeared in the second block (trials 21-40) in the negative condition.

Cerebellar reactivity. Despite being largely ignored and generally not discussed, imaging studies repeatedly indicate significant changes in cerebellar activity of patients with anxiety disorders compared to healthy controls. Close examination of the reported data reveals significant changes in the cerebellum during resting state and anxiety-provoking tasks in social anxiety disorder [180-182], post-traumatic stress disorder [183-187], obsessive compulsive disorder [188] and generalized anxiety disorder [189,190].

Individual differences in cerebellar reactivity have recently been extended to include anxiety vulnerability. Numerous studies assess the correlation between measures of anxiety vulnerability, most often trait anxiety, and brain activity [191]. Mostly, these studies report that individual differences in amygdala and PFC activity underlies trait anxiety, modulating stimulus processing and increasing hypervigilance [192-195]. What is often overlooked is that reciprocal connections between the cerebellum, prefrontal cortex, and amygdala position the cerebellum to modulate reactivity in anxiety vulnerable individuals. In the only published study to date to our knowledge that discusses cerebellar activity and temperament, Blackford and colleagues [10] compared behaviorally inhibited to uninhibited individuals when viewing familiar and novel faces and found significant increases in BOLD activation in the right cerebellum of the inhibited individuals when viewing novel faces. Specifically, they reported significant increases in the right Crus 1/Lobule VI region of the cerebellum, which may be related to processing the valence of emotional cues, salience detection, and in sensory processing and expectation; especially pain-related processes like fear and startle reactions [2,11,76].

The cerebellar differences found in the Blackford study were the result of a full-brain analysis; importantly, standard imaging procedures often incompletely image the cerebellum, so it is possible that the entire structure is not included in typical analyses. Recent research in our lab has explored the relationship of cerebellar activity and anxious temperament as measured by behavioral inhibition and trait anxiety. To extend the Blackford study we again used familiar faces and novel faces. Additionally, we used familiar and novel scenes, allowing us to differentiate the effect of social stimuli and novelty. Furthermore, we used the cerebellum as our region of interest, ensuring complete coverage during imaging. Finally, participants underwent eyeblink conditioning in addition to imaging (outside of the scanner). Given what is known about the behavioral profile of behaviorally inhibited individuals and in light of previous research, we hypothesized that high behavioral inhibition would correlate with changes in cerebellar activity, with the strongest differences occurring to novel faces. We found that the group with higher scores on measures of behavioral inhibition [168,169] had greater cerebellar reactivity to the novel faces compared to baseline than those with lower scores, a difference not seen with familiar faces. Additionally, we observed greater activity of the high BI group when viewing novel scenes, suggesting that the cerebellum may be sensitive to novel stimuli in general. Differences in percent signal change and BOLD signal activations can be seen in figure 4. In eyeblink conditioning, individuals with high BI scores acquired delay eyeblink faster than those with low scores, replicating previous work in our lab.

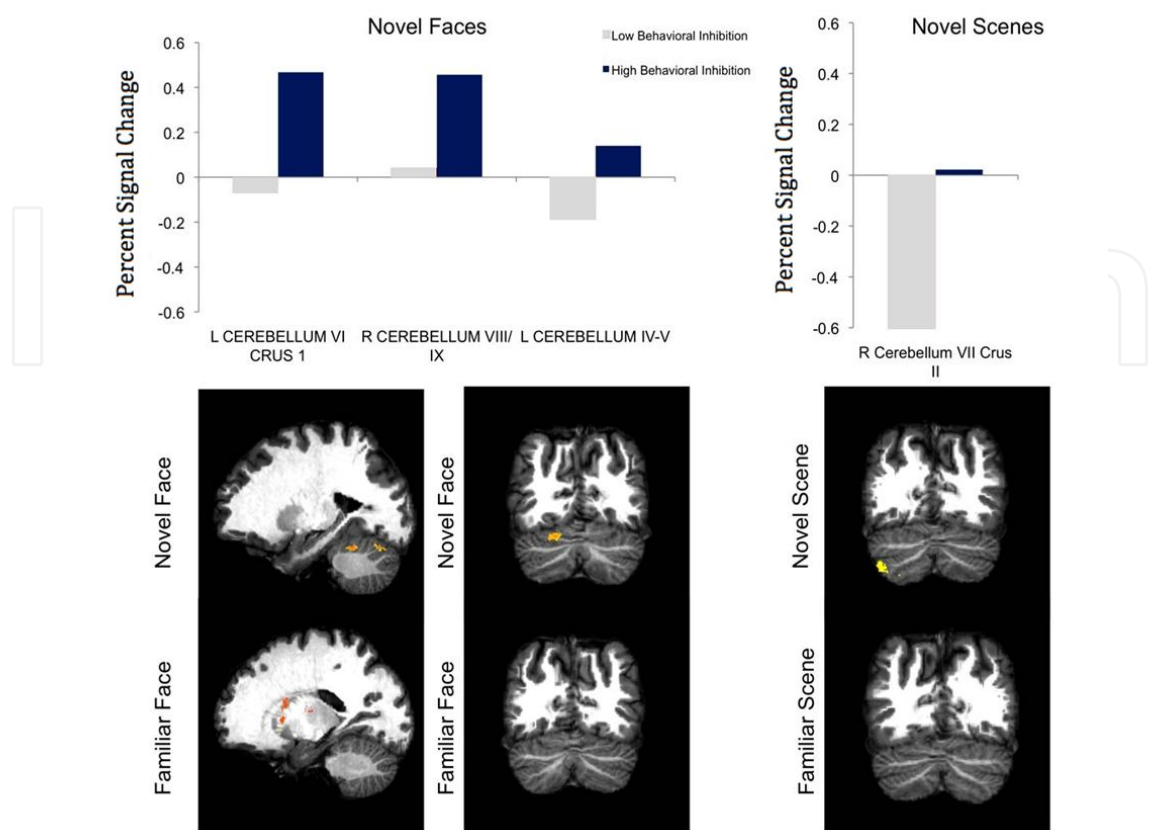


Figure 4. Increased cerebellar reactivity to novel stimuli in anxiety vulnerable individuals. Healthy, college-aged students who scored high on measures of behavioral inhibition demonstrated increased reactivity to multiple areas of the cerebellum in response to novel faces compared to baseline. A similar differential increase in activity was seen for novel scenes. Significant differences in cerebellar activity from baseline were not seen in the familiar face or familiar scene conditions. Left is Right.

We have demonstrated individual differences in cerebellar reactivity and behavior in cerebellar-modulated tasks related to anxiety and anxiety vulnerability. By modulating the signal from higher cortical areas, the cerebellum may be involved in processes related to emotion and anxiety. Figure 5 outlines the cerebrocerebellar and corticopontinecerebellar circuitry as well as the cerebellar outputs for eyeblink conditioning, heart rate responsivity, and higher cognitive process. Cerebellar outputs to prefrontal regions such as the DLPFC and ACC would allow it to modulate incoming signals to these areas regarding higher cognitive functioning including emotion and anxiety. The anatomical pathways, functional connectivity, and individual differences observed of both clinical anxiety and anxiety vulnerable individuals suggest a cerebellar role in anxiety disorders. We propose that cerebellar functioning is another risk factor that needs to be added to the diathesis of anxiety vulnerability. Continued research of individual differences in both cerebellar-modulated tasks (e.g., eyeblink) and the cerebellar role in higher cognitive tasks (e.g., stimulus processing, attention; emotional regulation) will shed light on the interplay of vulnerabilities contributing to the development of anxiety disorders.

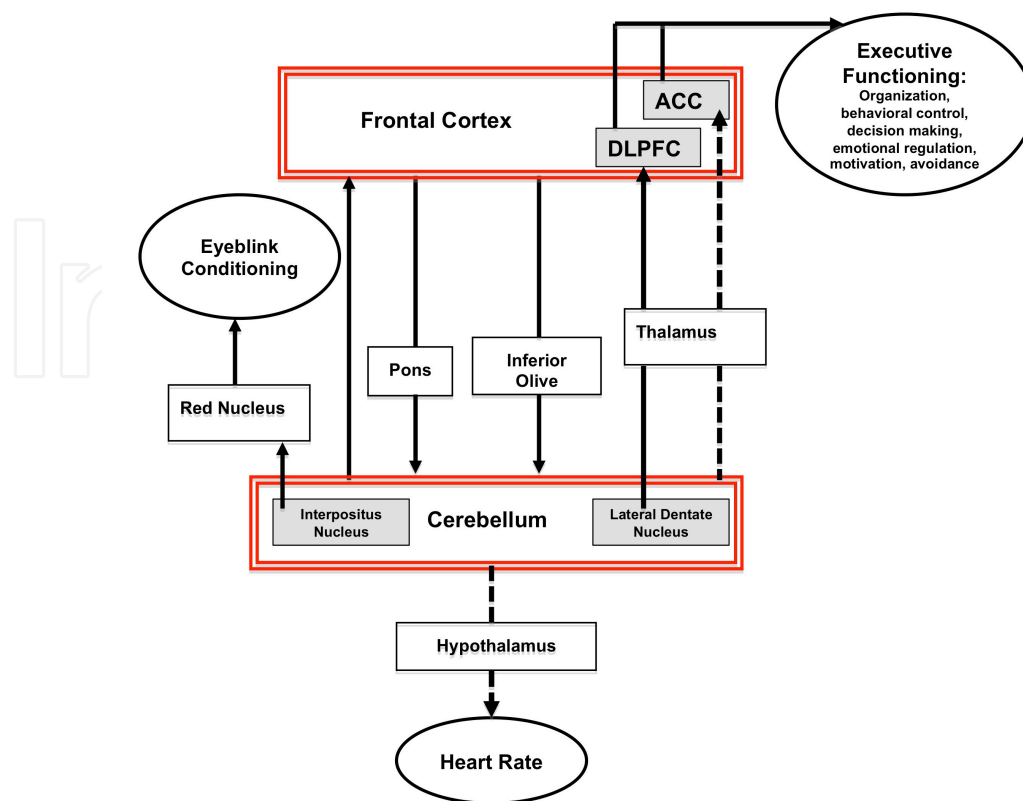


Figure 5. Cerebellar functional connectivity. Reciprocal connectivity with the cortex puts the cerebellum in a position to modulate higher cognitive processes via connections with the dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC). Many functions altered by at-risk temperament may be modulated by the cerebellum including eyeblink conditioning, heart rate reactivity, and executive functioning such as emotional regulation, motivation and avoidance.

Author details

Meghan D. Caulfield and Richard J. Servatius*

*Address all correspondence to: Richard.Servatius@va.gov

Stress & Motivated Behavior Institute, New Jersey Medical School, New Jersey, U. S. A.

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