FUNCTIONAL NEUROLOGY SEMINARS

Cerebellum and Immunity

As mentioned in last week's post, the cerebellum has several roles within the neuraxis including sensory information integration, learning motoric movements, modifying movements, controlling mood, affect, emotion and regulating immune functions. Previously, we have discussed how depression can be linked to immune dysregulation, sugar dysregulation and lack of exercise. I mentioned last week that exercise will increase the frequency of firing of the cerebellum. I also mentioned that the cerebellum may play a role in higher cognitive functions such as mood, affect and cognition. This week I would like to bring some of those concepts together with a central focus on the cerebellum's role in immune function and how it relates to mood and affect.

Remember, if a patient states that they are depressed, it is always important to ask yourself: what is causing the depression? As mentioned earlier, the literature shows that depression is a multimodal and very complex problem. The literature also shows that approximately 30-50% of patients that suffer from depression are not responsive to antidepressant management. It is difficult to pinpoint one specific causative factor when it comes to depression. So far we have discussed the following considerations: decreased activation of frontal lobes, decreased activation of the cerebellum, decreased exercise, immune system dysregulation, gut inflammation creating central consequences and sugar dysregulation causing central consequences.

As mentioned in my week two post, the hypothalamus plays a role in depression through the hypothalamic-pituitary-adrenal axis (HPA). The hypothalamus can also play a role in depression when looking at it's communication with the cerebellum. We know that depression lives in the frontal lobe and the frontal lobe communicates with the cerebellum all the time. The cerebellum also communicates very frequently with the hypothalamus, an area that plays a significant role in immune regulation. The frontal lobe and hypothalamus also communicate all the time. So once again we have this cross-talk between the frontal lobes, cerebellum and hypothalamus. If one area is not working well, then it is quite possible that there will be break down, functional lesions or negative plasticity in these other areas as well.

In recent literature, it has been hypothesized that cerebellar immunomodulation exists and it may be mediated by the hypothalamus. Anatomically, there is no direct connection between the cerebellum and the immune system. There is, however, a direct projection from the cerebellum to the hypothalamus named the cerebellohypothalamic projections. If the hypothalamus is important in immune regulation, then this pathway may serve as an important mediator in modulating the immune system and if the cerebellum has immunomodulatory properties, then the cerebellum may have an indirect effect on depression (by altering immune function).

Take Home Points:

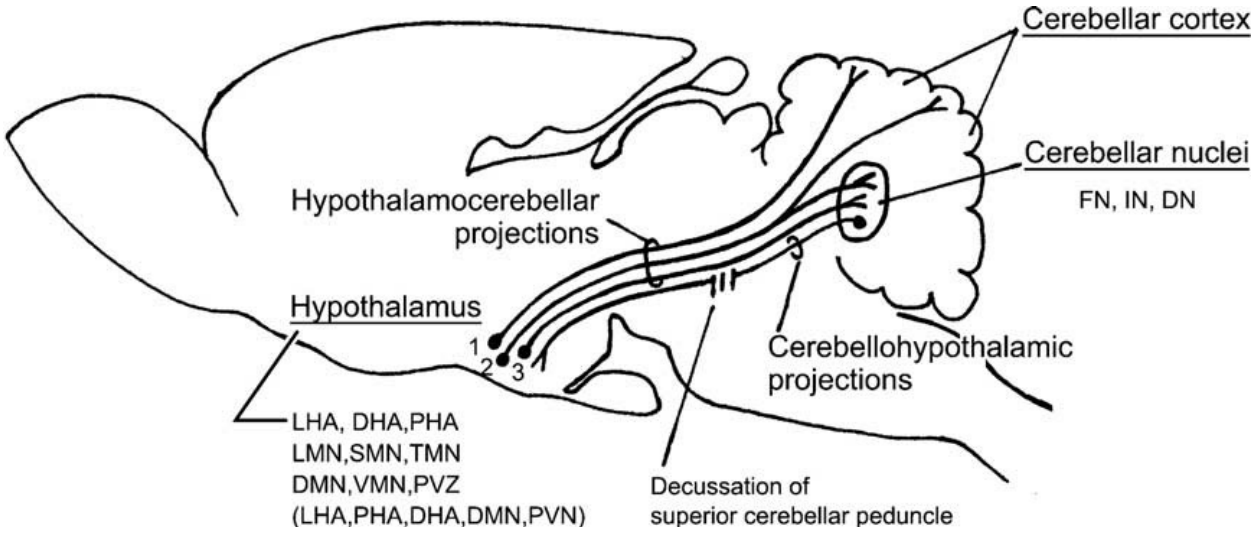
-Immune dysregulation has been shown in the literature to be a contributing factor to depression.

-The frontal lobe, hypothalamus and cerebellum all communicate with one another, if one area is not working well, another may be compromised.

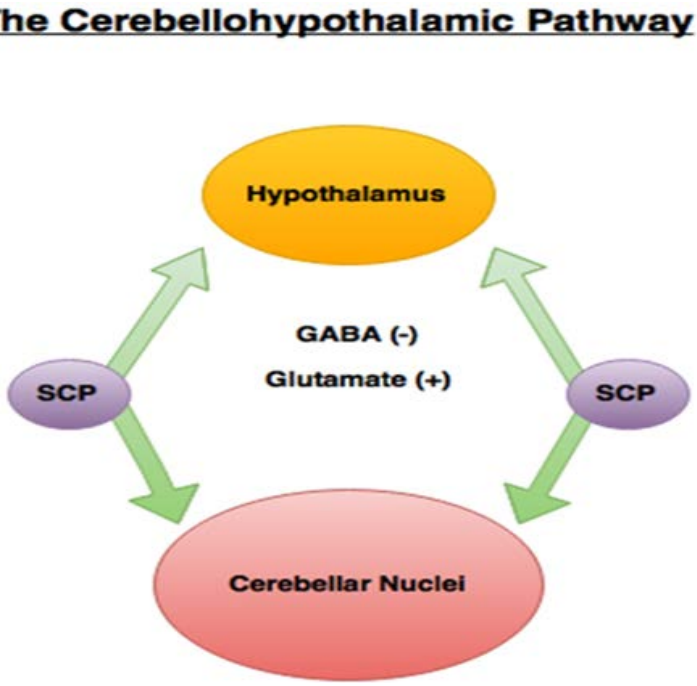
-Although there is not a direct pathway between the cerebellum and the immune system, the cerebellum plays a role in immunomodulation by communicating with the hypothalamus.

Projections from the cerebellum to the hypothalamus come from the three nuclei I discussed last week: the fastigial nucleus in the most medial portion of the cerebellum, the interposed (composed of the globus and emobliform) and the dentate (the most lateral nucleus). These projections travel through the superior cerebellar peduncle to different areas in the hypothalamus including the lateral, posterior and dorsal hypothalamic areas, as well as the dorsomedial and paraventricular nuclei. The hypothalamus then sends the information to immune cells using the peripheral pathways of the sympathetic and endocrine systems.

The diagram below shows the anatomical relationship between the cerebellar nuclei and the projections to the specific areas in the hypothalamus:



It has been shown in recent literature that there are glutamatergic projections from the interposed nucleus and GABA-ergic projections from the interposed and fastigial nucleus in the cerebellum to the lateral hypothalamic area. Lesions in the interposed nucleus have been shown to attenuate the functions of T, B and natural killer cells while lesions in the fastigial nuclei have been shown to enhance the functions of T, B and natural killer cells as well as differentiation of thymocytes. Below is an example of the bidirectional communication between the hypothalamus and the cerebellum:



The fact that the cerebellum plays an important role in immunomodulation again shows just how diverse and how significant it is to the overall health and function of the patient. Modulation of the immune system can mean that either good or bad things are happening. If modulation of the immune system means that there is increased inflammation, then what we have already talked about rings true, immune dysregulation can lead to increased inflammation which can lead to psychiatric disorders such as alterations in mood and depression.

Take Home Points:

-In recent literature, creating "lesions" in certain nuclei of the cerebellum have proved to make changes in immune regulation.
-The cerebellum plays a role in the inflammatory response
-The inflammatory response has a significant impact on mood and affect.

The Cerebellum and Autoimmunity:

This is something I want to expand on in future posts but it warrants mention here. There are several ways to assess the cerebellum in clinical practice (I will make a short list below). If a patient presents with a lot of cerebellar signs, it may be a good idea to run labs on the patient. Signs and symptoms of cerebellar dysfunction include, but of course are not limited to: difficulty with balance, nausea, coordination issues (remember both in movement and thoughts (dysmetria of thought)), anxiety, vertigo, etc.

Anatomical and/or functional lesions of the cerebellum may be the cause of these signs and symptoms. Let's say as a functional neurologist you are treating a patient with all of the signs/symptoms listed above. The patient is making great strides towards health under your care, however, anxiety and vertigo are slightly persisting. First of all, kudos to you because now that we know how fantastic and important the cerebellum is, the patient's health and well-being are that much greater under your care. Running a few labs on the patient may change the course of care for your patient and help in knocking out these pesky persistent symptoms.

One lab that does a great job of testing for autoimmunity is Cyrex Labs. If a patient has persistent cerebellar signs while undergoing treatment, a good lab to run is Cyrex's Array 5. Array 5 tests for multiple tissue autoimmunity including Cerebellar IgG and IgA and also Glutamic Acid Decarboxylase 65 (GAD-65) IgG and IgA (which have been seen in patients suffering from cerebellar ataxia). What do we do if the test is positive? Let's go back to the patient with functional cerebellar dysfunction. The neurologically specific exercises have made great strides towards their health but now we know the patient is suffering from an autoimmune attack to self tissues. They have lost "self tolerance." In order for the patient to reach optimal cerebellar performance, the inflammation has to be addressed. I will expand on this in next weeks post. I just wanted to give a short example of why blood work can be very important when looking into the patient's best interest, especially if their treatment has hit a plateau.

Remember the glutamatergic and GABA-ergic projections between the cerebellar nuclei and the hypothalamus? GAD is an enzyme that helps turn glutamate (an excitatory neurotransmitter) into GABA (the major inhibitory transmitter). If the patient has GAD antibodies, there will be alterations in the immunomodulatory projections from the cerebellum to the hypothalamus, thus changing the immune response. Once again, this can lead to altered immunoregulation which can lead to inflammation, which can lead to depression. Of course there are more immune panels that can be ran but if we see that the patient is suffering from a condition that is autoimmune in nature then it would be in everyone's best interest to treat the patient for their autoimmune condition either before or simultaneously during their specific rehabilitation exercises. For more information on inflammation, check out Spencer Zimmerman's and Caleb Greer's posts from weeks past. They cover a lot of great information. Ok how do we assess cerebellar fuction?

Assessing the Cerebellar Function:

From a functional neurological perspective, you can test for functional breakdown in different areas of the cerebellum. The vermal, or midline region of the cerebellum deals with midline structures such as the eyes, spine, vestibular system and head position. Lesions may include:

- Stance and Gait Abnormalities (Wide Stance)
- Balance Difficulty
- Poor Heel-Shin Test
- Disturbed Eye Movements
- Nystagmus or Hypermetric Saccades
- Altered Head Positions

The intermediate portion of the cerebellum presents with a combination of midline and lateral cerebellar lesions. Most specifically you can test rapid alternating movements from the shoulder girdle and looking for breakdown on one side compared to the other (dysdiadochokinesia). When testing the lateral region of the cerebellum, lesions may include:

- Gait or stance abnormalities (shifting weight)
- Decomposition of Limb Movements
- Dysmetria
- Dysdiadochookinesia
- Appendicular Ataxia
- Kinetic and Static Tremor
- Dysarthria
- Hypotonia
- Dyssynergia

Next week I will provide some specific information on how to perform neurological testing for the cerebellar lesions mentioned above, more correlating bloodwork tests, some expanded lab panels that explore inflammation and tying them back into their effects on mood and affect. More people suffer from some degree of depression than we may think, and remember, when one of these areas are not up to par, other areas suffer.

Below is a nice summary of neuroinflammation I found that relates to the inflammatory response and depression (just wanted to add this in for nice visual effects):

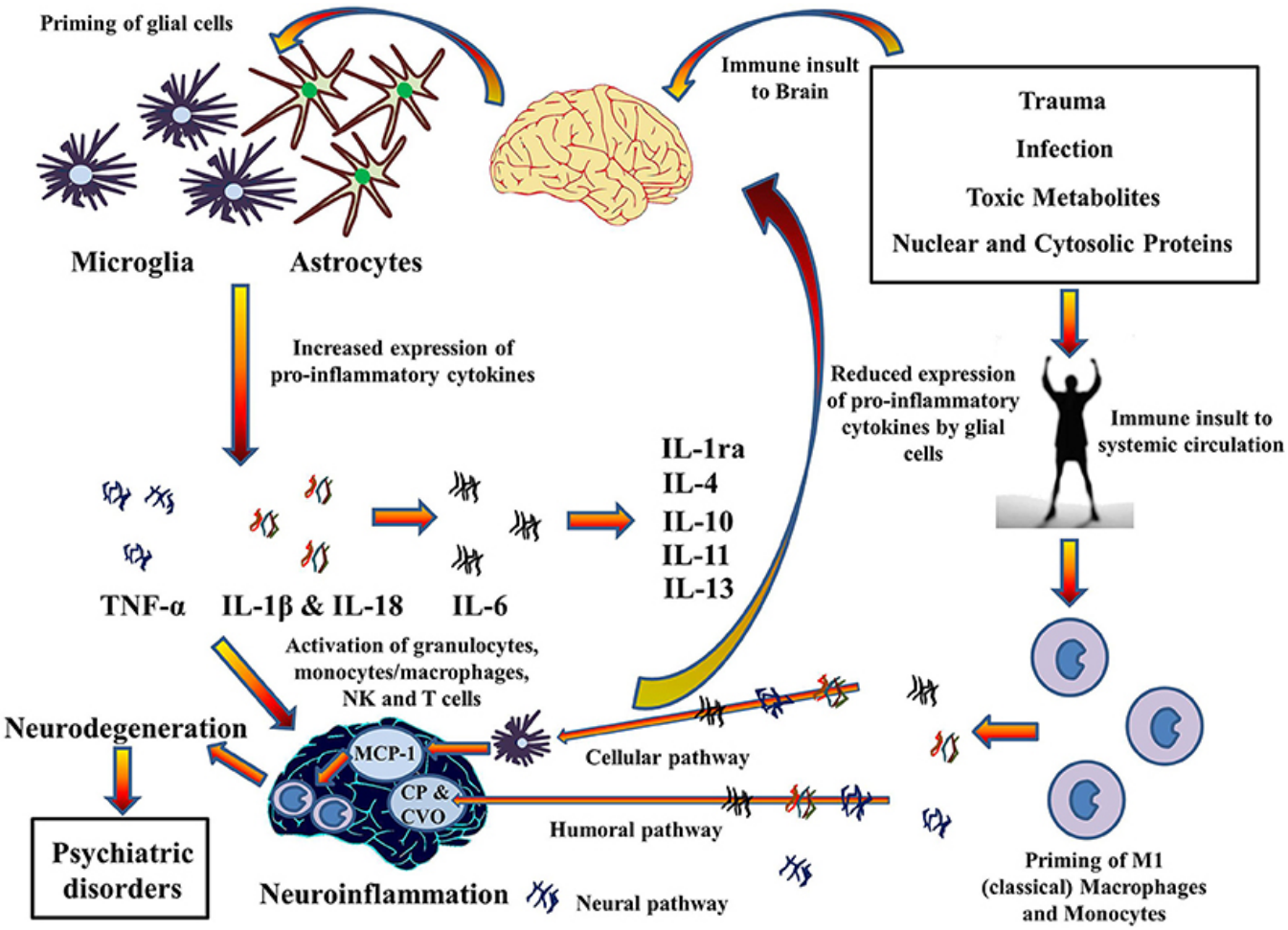


Diagram retrieved from: http://journal.frontiersin.org/article/10.3389/fnins.2014.00315/full

**Shout out to Dr. Elias Druckman for helping me with the research on this topic.

References

Bayreuther, C., Hieronimus, S., Ferrari, P., Thomas, P., & Lebron, C. (2008). Auto-immune cerebellar ataxia with anti-GAD antibodies accompanied by de novo late-onset type 1 diabetes mellitus. Diabetes Metab, 34(4), 386–388. doi:10.1016/j.diabet.2008.02.002

Lu, J., Mao, H., Cao, B., & Peng, Y. (2012). Effect of Cerebellohypothalamic Glutamatergic Projections on Immune Function. Cerebellum, 11, 905–916. doi:10.1007/s12311-012- 0356-8

Ni, S.-J., Qiu, Y.-H., Lu, J.-H., Cao, B.-B., & Peng, Y.-P. (2010). Effect of cerebellar fastigial nuclear lesions on differentiation and function of thymocytes. Journal of Neuroimmunology, 222, 40–47. doi:10.1016/j.jneuroim.2010.02.017

Peng, Y.-P., Qiu, Y.-H., Chao, B.-B., & Wang, J.-J. (2005). Effect of lesions of cerebellar fastigial nuclei on lymphocyte functions of rats. Neuroscience Research, 51, 276–284. doi:10.1016/j.neures.2004.11.010

Wang, F., Cao, B., Liu, Y., Peng, Y., & Qiu, Y. (2010). Role of Cerebellohypothalamic GABAergic Projection in Mediating Cerebellar Immunomodulation. International Journal of Neuroscience, 121, 237–245. doi:10.3109/00207454.2010.544431

Zhu, J.-N., Yung, W.-H., Kwok-Chong Chow, B., Chan, Y.-S., & Wang, J.-J. (2006). The cerebellar-hypothalamic circuits: Potential pathways underlying cerebellar involvement in somatic-visceral integration. Brain Research Reviews,52, 93–106. doi:10.1016/j.brainresrev.2006.01.003