**On correcting a centuries-old dogma: a rooster’s great tragedy and our great gain**

Scientists might spend more time correcting assumptions than making discoveries. Not long after the gross anatomists had identified the hefty, lobular structure at the base of the brain as the cerebellum, the overenthusiastic phrenologists of the late 1700s had arbitrarily given the region a clear and specific function: philoprogenitiveness (love of making babies). This was in part based on how cold compresses to the back of the head appeared to cure habitual masturbation1.

Of course, phrenology was rapidly and completely discredited by the experimental sciences. To determine what the cerebellum might actually do, scientists in the 1800s removed the structure from the brain and carefully observed how animals behaved after the surgery. Pierre Fluorens favored experimenting in birds—chickens in particular. Upon removal of his rooster’s cerebellum, Fluorens noted that the bird still seemed very much interested in hens, but its deficits in motor coordination made it tragically difficult to express that interest. From his experiments Flourens concluded:

*“… all movements persist following ablation of the cerebellum: all that is missing is that they are not regular and coordinated…”*

Experiments like this have led to the general framework that the cerebellum is purely a structure that coordinates movements. As a testament to the thoroughness of this work, it has remained the standard since Fluorens’ time1-3.

Only recently have we been rigorously revisiting those assumptions. This is in large part motivated by clinical work, where patients with identified and specific insults (stroke, trauma, etc.) to the cerebellum have much more than motor dysfunctions. Hidden behind the more obvious motor symptoms, these nonmotor symptoms were so numerous and consistent that they are now known as the Cerebellar Cognitive Affective Syndrome, a set of symptoms ranging from language dysfunction to problems interpreting social cues3,4. Meta-analyses of autistic populations also revealed that one of the best predictors of autism later in life was damage to the cerebellum during infancy (second only to having an autistic twin)5. One of the most critical findings for the field was that selective expression of autism-related genes only in the cerebella of mice resulted in social deficits6. With these, we knew that the dysfunction of the cerebellum was sufficient to cause nonmotor dysfunction, but how might this occur?

Perhaps the cerebellum could modulate the known social circuitry within the brain. Innovations in optogenetics have given us the ability to manipulate activity in specific pathways in the brain, allowing us to assign functions to circuits in unprecedented ways. For example, the desire and ability to socialize has now been associated with the ventral tegmental area (VTA)7, an area known as the “brain’s pleasure center.” A simple hypothesis might be that the cerebellum could access the social circuitry and all sorts of nonmotor functions via a direct projection to the VTA.

Unfortunately, scant evidence of such a connection existed. The most recent anatomical mapping studies only had incidental observations or footnotes buried deep in supplemental data8,9. Nonetheless, our team used optogenetic tools to specifically label the connection from the cerebellum to the VTA of mice. To our surprise, the connection was not at all sparse, and was actually quite powerful: stimulating the cerebellar pathway to the VTA rapidly and robustly increased activity in the brain’s pleasure center. But was this relevant at a behavioral level?

To test this, we placed mice in a square room, and stimulated activity in the cerebellar pathway to the VTA only when the mouse entered one specific corner. Incredibly, mice would repeatedly visit that corner to get more stimulus. We did several more variations of this test but they all pointed to the same conclusion: stimulating this pathway was rewarding to the mice—perhaps even pleasurable. What could turning off the connection tell us?

Given the cerebellum’s recent history with social deficits, we decided to test whether turning off the connection would affect whether mice would choose to spend their time with other mice or investigating an object. When the cerebellar-VTA connection was taken offline, mice would lose their innate preference to socialize. Our final surprise was that none of these perturbations had any significant effects on the animals’ ability to move.

All this evidence pointed in the same direction: the cerebellum is much more than a motor structure, and might have specific pathways for nonmotor functions. Perhaps if we looked a bit more carefully at Fluorens’ rooster, we might find that the rooster lacked much more than motor coordination—maybe he actually lost the skills to hang with the other chickens. But this rooster’s tragedy is our gain: his dysfunctions have given us great insight into our own brains, opening doorways to understanding the human dysfunction.

1 Glickstein, M., Strata, P. & Voogd, J. Cerebellum: history. *Neuroscience* **162**, 549-559, doi:10.1016/j.neuroscience.2009.02.054 (2009).

2 Fine, E. J., Ionita, C. C. & Lohr, L. The history of the development of the cerebellar examination. *Semin Neurol* **22**, 375-384, doi:10.1055/s-2002-36759 (2002).

3 Schmahmann, J. D. The cerebellum and cognition. *Neurosci Lett* **688**, 62-75, doi:10.1016/j.neulet.2018.07.005 (2019).

4 Schmahmann, J. D. & Sherman, J. C. The cerebellar cognitive affective syndrome. *Brain* **121 ( Pt 4)**, 561-579 (1998).

5 Wang, S. S., Kloth, A. D. & Badura, A. The cerebellum, sensitive periods, and autism. *Neuron* **83**, 518-532, doi:10.1016/j.neuron.2014.07.016 (2014).

6 Tsai, P. T., Hull, C., Chu, Y., Greene-Colozzi, E., Sadowski, A. R., Leech, J. M., Steinberg, J., Crawley, J. N., Regehr, W. G. & Sahin, M. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. *Nature* **488**, 647-651, doi:10.1038/nature11310 (2012).

7 Gunaydin, L. A., Grosenick, L., Finkelstein, J. C., Kauvar, I. V., Fenno, L. E., Adhikari, A., Lammel, S., Mirzabekov, J. J., Airan, R. D., Zalocusky, K. A., Tye, K. M., Anikeeva, P., Malenka, R. C. & Deisseroth, K. Natural neural projection dynamics underlying social behavior. *Cell* **157**, 1535-1551, doi:10.1016/j.cell.2014.05.017 (2014).

8 Beier, K. T., Steinberg, E. E., DeLoach, K. E., Xie, S., Miyamichi, K., Schwarz, L., Gao, X. J., Kremer, E. J., Malenka, R. C. & Luo, L. Circuit Architecture of VTA Dopamine Neurons Revealed by Systematic Input-Output Mapping. *Cell* **162**, 622-634, doi:10.1016/j.cell.2015.07.015 (2015).

9 Watabe-Uchida, M., Zhu, L., Ogawa, S. K., Vamanrao, A. & Uchida, N. Whole-brain mapping of direct inputs to midbrain dopamine neurons. *Neuron* **74**, 858-873, doi:10.1016/j.neuron.2012.03.017 (2012).