of granule cells? The fact that induction of this form of LTP does not require coincident postsynaptic depolarization suggests that it may not be selective, and if so, it would be expected to lead to gross changes in all output synapses of mossy cells that undergo sustained burst firing. However, specificity could be achieved if the expression or subcellular targeting of postsynaptic TrkB receptors in granule cells was itself variable and/or modulated by activity. The current results, however, would also be consistent with this mechanism playing a more homeostatic role, adjusting the overall balance of dentate excitation and inhibition to achieve a target degree of sparsity in the network representation of space, for example. It will be important to determine how the spatial map encoded by granule cells depends on their coordinated activation by both mossy cell feedback and spatially tuned input from entorhinal cortex. Indeed, as long as each new insight into the function of dentate mossy cells raises more questions, these fascinating neurons will continue to be attractive candidates for future investigation. In other words, mossy cells will ensure that neuroscientists will have to keep rolling to gather no moss.

REFERENCES

Danielson, N.B., Turi, G.F., Ladow, M., Chavlis, S., Petrantonakis, P.C., Poirazi, P., and Losonczy, A. (2017). Neuron *93*, 552–559.e4.

GoodSmith, D., Chen, X., Wang, C., Kim, S.H., Song, H., Burgalossi, A., Christian, K.M., and Knierim, J.J. (2017). Neuron *93*, 677–690.e5.

Hashimotodani, Y., Nasrallah, K., Jensen, K.R., Chávez, A.E., Carrera, D., and Castillo, P.E. (2017). Neuron *95*, this issue, 928–943.

Hsu, T.T., Lee, C.T., Tai, M.H., and Lien, C.C. (2016). Cereb. Cortex *26*, 2715–2727.

Jinde, S., Zsiros, V., Jiang, Z., Nakao, K., Pickel, J., Kohno, K., Belforte, J.E., and Nakazawa, K. (2012). Neuron *76*, 1189–1200.

Lysetskiy, M., Földy, C., and Soltesz, I. (2005). Hippocampus *15*, 691–696.

Ratzliff, Ad., Howard, A.L., Santhakumar, V., Osapay, I., and Soltesz, I. (2004). J. Neurosci. *24*, 2259–2269.

Scharfman, H.E. (2016). Nat. Rev. Neurosci. *17*, 562–575.

Senzai, Y., and Buzsáki, G. (2017). Neuron *93*, 691–704.e5.

Weisskopf, M.G., Castillo, P.E., Zalutsky, R.A., and Nicoll, R.A. (1994). Science *265*, 1878–1882.

The Strange Case of Aggression and the Brain

Vinicius M.A. Carvalho,[1] Thiago S. Nakahara,[1] and Fabio Papes[2,*]
[1]Graduate Program in Genetics and Molecular Biology
[2]Department of Genetics and Evolution
Institute of Biology, University of Campinas, Rua Monteiro Lobato, Campinas, Sao Paulo, 13083-862, Brazil
*Correspondence: papesf@unicamp.br
http://dx.doi.org/10.1016/j.neuron.2017.07.041

Territorial male mice are aggressive toward intruding males, but socially bonded males are not. Through manipulation of activity in a subset of neurons in the ventromedial hypothalamus, Yang et al. (2017) report that social and physiological factors non-linearly interact to control male aggression.

In his book *The Strange Case of Dr. Jekyll and Mr. Hyde*, Robert Louis Stevenson portrays the story of a scientist who, through ingestion of a concocted potion of his own making, turns into his evil alter ego, characterized by "ape-like fury" and "remorseless rage." As usually happens with much literary discourse, this narrative was inspired by ideologies and perspectives of the time in which it was written. We can now envision it as representative of the notion that human beings are genetically predisposed to aggressive behavior and that a simple trigger is enough to erase any socially determined barriers, to bring the individual back to a state of primal, feral temperament.

Even Darwin was friends with the idea that behavioral traits are the result of hard-wired biological programs that are predominantly inherited. He wrote, "I am inclined to agree with Francis Galton in believing that education and environment produce only a small effect on the mind of any one, and that most of our qualities are innate" (Darwin et al., 1959). The drive to understand human emotions and behaviors is as old as mankind itself. Over time, science figures such as Sigmund Freud, B.F. Skinner, and others added additional ways of thinking about the influence of nature (biological determination) versus nurture (environment) on behavior and personality. Although the debate has been declared as outdated by most social scientists and some biologists, the "nature *versus* nurture" dichotomy remains in biological literature as a simple model upon which to explore the contributions of genetic underpinnings and environment on behavioral output.

The beauty of science is that, as hard evidence accumulates and new ideas and methodological approaches arise, old problems can be scrutinized under new light and in great detail. In this issue of *Neuron*, Yang and colleagues in Dr. Nirao Shah's group have explored the contributions of environmental and physiological variables on behavior by studying aggression in the laboratory

mouse (Yang et al., 2017). When a male mouse establishes dominance over a territory (residence), it becomes aggressive toward other intruding males, an effect dependent on aggression-inducing pheromones emanating from the intruder (Chamero et al., 2007; Leypold et al., 2002; Stowers et al., 2002). Strikingly, this behavioral output is innate, in the sense that no prior experience or learning is necessary. In contrast, other types of interaction involving a male do NOT result in aggressive displays: for example, males never attack a female, and males that occupy a certain territory as a social group (usually driven away by a dominant male in the vicinity) are not aggressive toward intruders (Crowcroft and Rowe, 2009). This flexibility is obviously adaptive, because it is important for a male to spend energy defending territory if it is his to keep, but not justified if he is just submissively co-habitating with another dominant male. Importantly, if male aggression is innate but flexible, what then is the neural basis for such flexibility? Even in the laboratory setting, it seems that triggering of an innate behavior may be largely dictated by internal and external contexts.

During the last decades, great effort has been undertaken to describe and manipulate the neural pathways controlling aggression and many other behaviors in animal models. It has long been known that the hypothalamus is critically relevant for the generation of aggression in mammals (Kruk et al., 1983). More recently, Dr. David Anderson's group at Caltech identified a specific sub-region in the ventromedial nucleus of the hypothalamus (VMH) as a brain site functionally linked to inter-male aggression in the mouse (Lin et al., 2011). This region is characterized by cells expressing estrogen and progesterone receptors. It became clear that such neurons are necessary for male mice to engage in aggressive encounters with other males, because optogenetic inhibition or genetic ablation of such hypothalamic subpopulation results in the loss of aggression (Lin et al., 2011; Yang et al., 2013).

Other experiments showed that optogenetic activation of estrogen-receptor-positive VMH cells resulted in aggressive bouts in male mice: whenever the target hypothalamic neurons were illuminated, aggression was displayed, even in contexts in which aggression would not be elicited, such as during interaction with females (Lee et al., 2014; Lin et al., 2011). These data showed that activation of certain sub-regions of the VMH is sufficient to trigger aggression, leading to the notion that this is an aggression command center—a set of decision-making neurons that, when active, lead to a complete and coordinated sequence of aggressive behavioral patterns. According to this view, the VMH should act as the sole determinant for aggressive behavior to emerge, as the function of a genetically pre-programmed circuit. Just like the target for Dr. Jekyll's transforming potion would!

The problem is that most of these ideas stemmed from experiments conducted under limited or conditional variables. For example, in most assays, the VMH was artificially activated only in singly housed males; additionally, these tests used optogenetics fibers, which may have encumbered mouse movement (Lee et al., 2014; Lin et al., 2011). Yang et al. (2017) now challenged the assumption that the VMH is an on-off switch for male aggression, by applying chemogenetics to investigate the behavior in a much more naturalistic paradigm, using a test known as the resident-intruder assay. This approach allowed the authors to controllably vary internal and external circumstances, including the subject's social experiences, the gender and social status of the mouse opponent, sensory input, and the organism's internal hormonal state. The results painted a much more complex picture of the hypothalamus than previously imagined: the generation of even such simple, directed, and purposive behavior as male aggression is greatly impacted by the organism's internal state and prior experiences, chief among them social bonding. Importantly, the data made it clear that the VMH is not a classical command center: interaction between different signals non-linearly dictates the likelihood that the behavior be generated, some of which acts upstream and some of which operates downstream of the hypothalamus.

Yang and colleagues adopted a DREADD chemogenetics approach to specifically activate progesterone receptor-expressing cells in the VMH (VMH_{PR}) by making them produce an exogenous receptor that can be controllably activated by a synthetic drug (any similarity to Dr. Jekyll's potion is a mere coincidence). First, they used this approach to show that activation of VMH_{PR} is sufficient to induce aggression in solitary males that are dominant over their territory (residents). VMH_{PR} activation increases the likelihood that aggression ensues in contexts where residents naturally attack other males, that is, in the presence of an intruding male (Figure 1A); in accordance with old data, VMH_{PR} activation produces aggression even toward opponents against whom this behavior would not normally be exhibited, such as in resident males toward females and in singly housed intruding males toward residents (Yang et al., 2017). Also, VMH_{PR} activation was shown to override factors that are essential for aggression, such as the need for testosterone and the ability to smell, because aggressive action is produced even in castrated or anosmic resident males.

The study then takes an interesting turn to investigate the lack of aggression in group-housed, socially bonded males. Normally, these mice do not attack other individuals placed as intruders into their home cage (or when facing another male in a neutral arena) (Figure 1B, top). Again, VMH_{PR} chemogenetic activation by the synthetic drug overrides the neural decisions that result in lack of aggression, eliciting attack toward the opponent (Figure 1B, bottom).

Up to this point, it would appear as though these experiments concur with the idea that the VMH is a command center for male aggression. However, this hypothesis succumbs to the next test conducted by Yang et al. (2017): they found that VMH_{PR} activation was NOT enough to induce aggression in socially bonded males inserted as intruders into another male's cage (Figure 1C, bottom), another situation in which these mice would not normally attack (Figure 1C, top).

This piece of result is very significant, not only because it supersedes the argument that the VMH commands aggression, but also because it shows that the neural decisions that lead to this behavior depend on the subject's territorial status: when the tested socially grouped animal is a resident, the VMH can override all

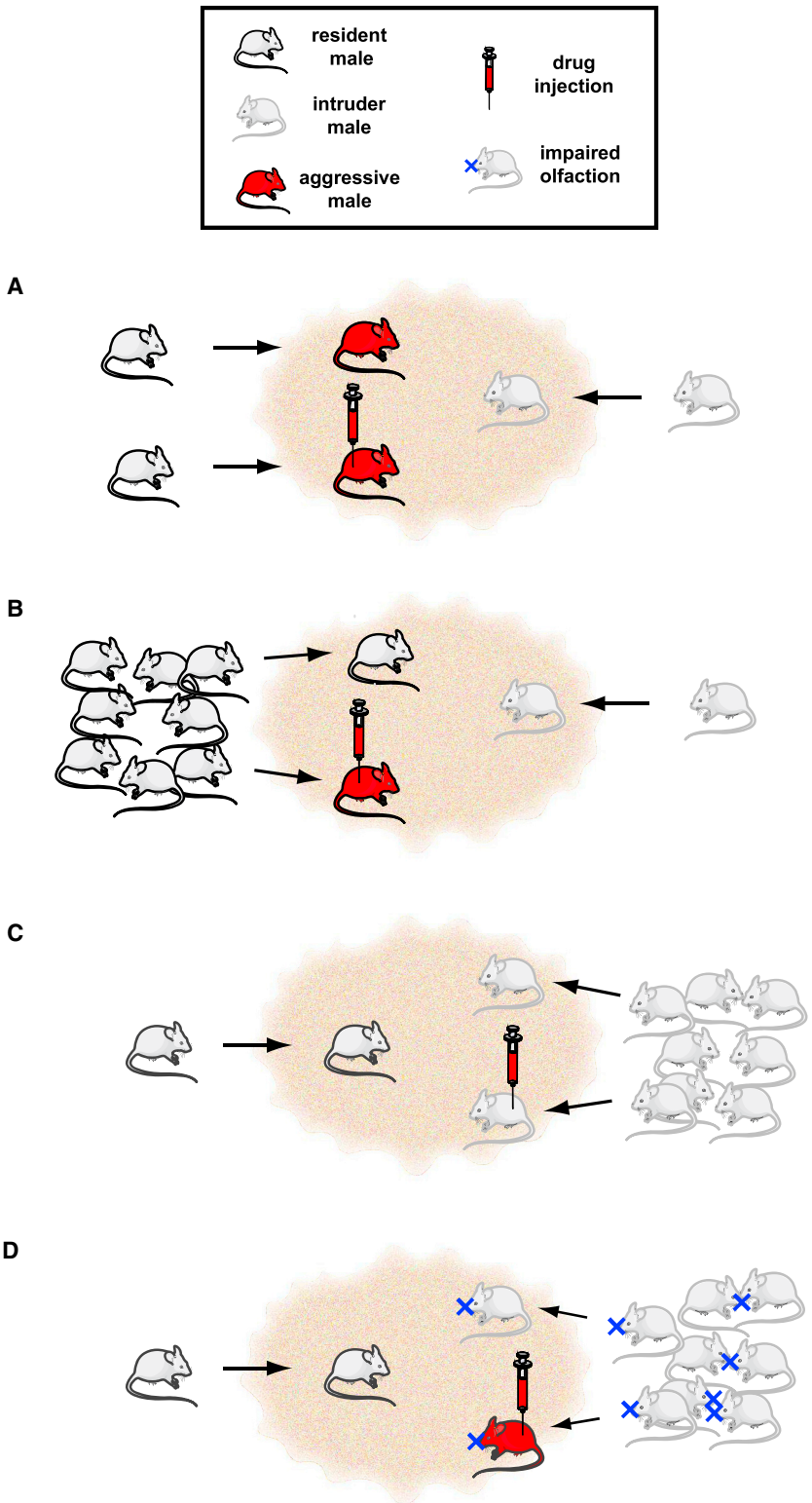

Figure 1. Influence of Social and Physiological Variables on Male Aggression
(A–D) Key experiments in Yang et al. (2017) investigating aggression in chemogenetic-manipulated (A) solitary residents, (B) socially bonded residents, (C) socially bonded intruders, and (D) anosmic socially bonded intruders.

other available information to command aggression, while it cannot do so in socially grouped subjects tested as an intruder (compare Figures 1B and 1C).

Like in Stevenson's novel, the paper's climax does not come until the end: in the last experiment, the subject animals were again socially bonded intruder males, but Yang et al. (2017) investigated what happens when olfaction is not working properly, that is, when potential olfactory signals are not detected. As opposed to the situation when olfaction is normal (Figure 1C), in mice without functional olfactory organs VMH_{PR} activation IS sufficient to induce aggression (Figure 1D, bottom). This is a very exciting piece of observation, indeed! It suggests that information provided by some sort of pheromone integrates with the VMH circuit (functionally downstream to it) to dominantly block the display of aggression in socially housed intruder males. Moreover, because none of these effects can be observed when the resident mouse is a female, the experiments further suggest that dominant males are the ones who emanate these aggression-blocking pheromones!

The most significant aspect of this paper is that it very elegantly explores an example of how the display of an adaptive behavior (male aggression, in this case) is dictated by the concerted integration of different environmental and physiological variables, including sensory input (pheromone detection), the organism's internal state (gonadal hormones), the individual's past experiences (social context), and biotic circumstance (the gender and social status of the mouse opponent).

Several avenues of investigation are obviously derived from this study. It appears as though the circuit involving the VMH computes internal and external information in a non-linear fashion, such that in certain circumstances the VMH acts like a command center for aggression, whereas in others it can be blocked by relevant sensory information. If this is true, how then is the circuitry behind these neural decisions organized? Which nucleus receives olfactory information coming from the sensory organs to later impede the generation of attack? It is likely that the brain and/or periphery differs between solitary and socially bonded males, in which case it will be exciting to

know how the circuits relevant to aggression work differently in these two biological contexts. Finally, the possibility of resident males releasing a special type of pheromone unbeknownst to science, capable of dominantly blocking aggression in socially bonded males, may initiate an area of investigation to purify and identify such molecular entity, describe the related sensory detectors, and study the circuit through which the associated information travels along the brains of non-aggressive, subdued males.

In the novel, a good number of people seek to understand the bizarre relationship between Dr. Jekyll and Mr. Hyde. Don't we all? One cannot help but wonder about the days when sophisticated techniques, reasoning, and objective experimentation will illuminate the processes through which genetic programs, neural circuits, inner drives, physiology, and social factors generate and modulate even the most complex of human behaviors, in sickness and in health. Humans can be aggressive, and the subject is dear not just to criminal psychologists, but to all of us. We wish to know. We want to understand. Olfaction may not be at play in human aggression, but the hypothalamus certainly is, and we wish to know if the same neural principles explain why and how we behave—that bit that makes us human. Perhaps, so did Dr. Jekyll.

REFERENCES

Chamero, P., Marton, T.F., Logan, D.W., Flanagan, K., Cruz, J.R., Saghatelian, A., Cravatt, B.F., and Stowers, L. (2007). Nature *450*, 899–902.

Crowcroft, P., and Rowe, F.P. (2009). Proc. Zool. Soc. Lond. *140*, 517–531.

Darwin, C., By, E., and Darwin, F. (1959). Yale J. Biol. Med. *32*, 141.

Kruk, M.R., Van der Poel, A.M., Meelis, W., Hermans, J., Mostert, P.G., Mos, J., and Lohman, A.H.M. (1983). Brain Res. *260*, 61–79.

Lee, H., Kim, D.-W., Remedios, R., Anthony, T.E., Chang, A., Madisen, L., Zeng, H., and Anderson, D.J. (2014). Nature *509*, 627–632.

Leypold, B.G., Yu, C.R., Leinders-Zufall, T., Kim, M.M., Zufall, F., and Axel, R. (2002). Proc. Natl. Acad. Sci. USA *99*, 6376–6381.

Lin, D., Boyle, M.P., Dollar, P., Lee, H., Lein, E.S., Perona, P., and Anderson, D.J. (2011). Nature *470*, 221–226.

Stowers, L., Holy, T.E., Meister, M., Dulac, C., and Koentges, G. (2002). Science *295*, 1493–1500.

Yang, C.F., Chiang, M.C., Gray, D.C., Prabhakaran, M., Alvarado, M., Juntti, S.A., Unger, E.K., Wells, J.A., and Shah, N.M. (2013). Cell *153*, 896–909.

Yang, T., Yang, C.F., Chizari, M.D., Maheswaranathan, N., Burke, K.J., Borius, M., Inoue, S., Chiang, M.C., Bender, K.J., Ganguli, S., et al. (2017). Neuron *95*, this issue, 955–970.