Journal Club

Editor's Note: These short reviews of recent *JNeurosci* articles, written exclusively by students or postdoctoral fellows, summarize the important findings of the paper and provide additional insight and commentary. If the authors of the highlighted article have written a response to the Journal Club, the response can be found by viewing the Journal Club at www.jneurosci.org. For more information on the format, review process, and purpose of Journal Club articles, please see http://jneurosci.org/content/preparing-manuscript#journalclub.

Laughter as a Neurochemical Mechanism Aimed at Reinforcing Social Bonds: Integrating Evidence from Opioidergic Activity and Brain Stimulation

Fausto Caruana
Unit of Neuroscience, University of Parma, 43125 Parma, Italy
Review of Manninen et al.

After more than two millennia of theorizing, a unified view of how laughter works is still lacking. Over the years, philosophers have proposed three predominant hypotheses to explain this peculiar human behavior: laughter is triggered by a feeling of superiority (superiority theory), by the appreciation of something that violates our expectations (incongruity theory), or by the release of nervous energy (relief theory; Morreall, 1987). More recently, some psychologists and anthropologists have suggested that laughter is, first and foremost, a means for social bonding and communication that evolved to change the behavior of others (Provine, 2000; Dunbar, 2012; Scott et al., 2014). We can dub it the social-bonding theory.

Despite the growing interest in understanding the social and cognitive bases of laughter, neuroscientific research tackling this topic is largely underdeveloped. There are at least two good reasons for this. First, being a social behavior, laughter disappears when isolated experimental subjects are scrutinized in a laboratory (Provine, 2000). This is nevertheless how experimentation in human cognitive neuroscience is usually performed, even when studying laughter. Second, laughter involves grimaces, vocalizations, and postural movements that produce artifacts when using imaging techniques. Hence, it is not surprising that most correlative studies of laughter focus on the visual or auditory perception of others' laughter.

In a recent study, Manninen et al. (2017) took a different approach to studying the social role of laughter from a neuroscientific point of view. Instead of studying the neural networks underpinning laughter production, they focused on the effects of laughter on the brain. Specifically, they investigated whether, and where in the brain, emitting social laughter results in opioid release. To avoid problems related to movement artifacts, subjects viewed comedy clips before undergoing PET scans with [^{11}C]carfentanil, a ligand specific to μ-opioid receptors (MORs). To enhance the emergence of social laughter, each subject watched the clips with two close friends. Control PET scans were performed on the same subjects after they spent a similar amount of time (30 min) alone in the testing room.

Whole-brain analyses showed that the production of social laughter increases opioid release in the anterior insula, the anterior cingulate cortex (ACC), and the posterior cingulate cortex (PCC), in addition to the basal ganglia and the thalamus. A decrease of opioid release, in contrast, was observed in the midcingulate cortex, which is often associated with affective aspects of pain perception (Vogt, 2005). None of these effects was observed during the control condition. Subsequently, the authors compared the amount of social laughter recorded in the pre-experimental manipulation with cerebral MOR availability, finding that the amount of social laughter was correlated with baseline MOR availability (i.e., the number of unoccupied receptors) in the ACC, PCC, orbitofrontal cortex (OFC), and ventral striatum (VS). This last result is particularly intriguing as it suggests that people with more MORs in these areas are more prone to engage in social laughter and, accordingly, that baseline MOR availability in these areas represents a potential tool in predicting the likelihood of inducing social laughter in a given subject.

In a previous study (Nummenmaa et al., 2016), the same group found that social touch—the possible human analog of primates grooming—increases MOR availability in a similar set of brain regions. Together, these results are particularly informative. Considering that grooming is thought to reinforce social structures, Manninen et al. (2017) speculate that (1) laughter evolved as an alternative mechanism for reinforcing social bonds in groups beyond those that can be maintained by grooming in primates (Dunbar, 2012) and (2) that this mechanism is mediated by opioid release in a network anchored to the brain structures mentioned above.

This view would bring further support to the social bonding theory of laughter. However, these results might be also accounted for by an alternative explanation. As recognized by Manninen et al. (2017), the lack of significant opioid release during the control

Received June 8, 2017; revised July 24, 2017; accepted July 27, 2017.
I thank Ahmad Jezzini and Giacomo Rizzolatti for valuable comments on a previous version of this article.
Correspondence should be addressed to Fausto Caruana, Unit of Neuroscience, University of Parma, Via Volturno 39, 43125 Parma, Italy. E-mail: fausto.caruana@unipr.it.
DOI:10.1523/JNEUROSCI.1589-17.2017
 0270-6474/17/378581-02$15.00/0

condition may be due to the absence of social interactions, rather than to the lack of laughter production. More generally, opioid release in the identified regions can be induced by a number of different pleasant sensations, independent of laughter and social contact. In line with this view, the ACC, a key region identified in the study by Manninen et al. (2017), is modulated by placebo and opioid analgesia (Petrovic et al., 2002), which are related to pleasant sensations but not to laughter or social interactions. Lacking a direct link between these regions and laughter, Manninen et al. (2017) cannot make a strong case for the link among neuroanatomy, laughter production, and opioid release but, rather, only for the following two independent statements: laughter results in opioid release; and opioid release modulates different brain regions. Additional evidence from other techniques are needed to add the missing piece to the puzzle.

According to Manninen et al. (2017), the rate of laughter bursts correlates with baseline MOR availability in the basal ganglia and, more specifically, in VS. Although this structure is associated with different rewarding and motivated behaviors independent of laughter, recent evidence showed that deep brain stimulation in the VS evokes mirthful smiling and laughter in patients with treatment-resistant obsessive-compulsive disorder (Gibson et al., 2017). Strikingly, VS stimulations that induce mirthful smiling also induce a modulation of the blood oxygenation level-dependent signal in several regions described by Manninen et al. (2017): the ACC, the anterior insula, the MD thalamus, as well as the frontal operculum. This latter region was not explicitly discussed in the study by Manninen et al. (2017), but see below for a possible involvement of frontal operculum in social laughter.

The contribution of the ACC to laughter is well established. A causal, rather than a merely correlative, role of ACC in laughter production has been shown in recent electrical stimulation studies in epileptic patients (Caruana et al., 2015). Stimulation of the pregenual sector of the ACC (pACC) evoke laughter along with a genuine feeling of mirth in half of the patients. Consistent with this, fMRI studies showed that the pACC is involved in the processing of happiness, while the subgenual sector of ACC is involved in sadness (Vogt, 2005; Saarimäki et al., 2016). The link among pACC, laughter, and social contagion is further strengthened by evidence that the same pACC site from which laughter has been elicited by electrical stimulation is also active during the observation of others' laughter, but not the observation of crying or neutral expressions (Caruana et al., 2017).

More intriguing is the role of the anterior insula. The authors interpret the contribution of the anterior insula as related to the processing of social touch, mediated by C-fibers. This seems like an unlikely interpretation, because C-fiber stimulation activates the dorsal posterior insula (Olausson et al., 2002) while MOR availability peaks in the anterior sector. An alternative interpretation is that MOR availability in anterior insula also includes the adjacent frontal operculum (Manninen et al., 2017, their Fig. 3), very close to the superior border of insula, and that both stimulation studies (Fernández-Baca Vaca et al., 2011; Caruana et al., 2016) and lesion studies (Lauterbach et al., 2013) associate with laughter and smile production—gating emotional input to the volitional communicative system.

Two additional regions where baseline MOR availability correlated with laughter production are PCC and OFC. Although PCC has been linked to happy feelings (Vogt, 2005; Saarimäki et al., 2016), and OFC is involved in the rewarding effects of affective social interactions, no studies have reported that laughter can be elicited by electrically stimulating these structures or impaired by their lesion. This suggests that the contribution of PCC and OFC to opioid release might be of a different kind. Conversely, some regions from which laughter has been elicited by electrical stimulation, such as the pre-SMA, the superior frontal gyrus (SFG), and the basal temporal lobe (BTL; for review, see Caruana et al., 2016), showed little or no laughter-induced opioid release, suggesting that their contribution to laughter likely concerns motor and semantic aspects, rather than social-bonding functions.

In conclusion, the study by Manninen et al. (2017) offers important support for the social-bonding theory of laughter and, more specifically, for the view that laughter evolved as a neurochemical mechanism to reinforce social bonds (Dunbar, 2012), with a reservation: the number of regions showing laughter-induced opioid release likely exceeds those specifically involved in social laughter. On the other hand, the number of regions that stimulation studies associate with laughter production surpasses the number of those specifically contributing to social laughter (e.g., pre-SMA, SFG, BTL). At the intersection between these two sets of evidence, only the pACC, the anterior insula/frontal operculum, and the VS appear to play a causal role in the production of social laughter. This raises the intriguing question of whether the remaining three philosophical theories of laughter focus on aspects of this behavior underpinned by different brain networks.

References

Caruana F, AvanziniP, Gozzo F, Francione S, Cardinale F, Rizzolatti G (2015) Mirth and laughter elicited by electrical stimulation of the human anterior cingulate cortex. Cortex 71:323–331. CrossRef Medline

Caruana F, Gozzo F, Pelliccia V, Cossu M, Avanzini P (2016) Smile and laughter elicited by electrical stimulation of the frontal operculum. Neuropsychologia 89:364–370. CrossRef Medline

Caruana F, Avanzini P, Gozzo F, Pelliccia V, Casaceli G, Rizzolatti G (2017) A mirror mechanism for smiling in the anterior cingulate cortex. Emotion 17:187–190. CrossRef Medline

Dunbar RI (2012) Bridging the bonding gap: the transition from primates to humans. Philos Trans R Soc Lond B Biol Sci 367:1837–1846. CrossRef Medline

Fernández-Baca Vaca G, Lüders HO, Basha MM, Miller JP (2011) Mirth and laughter elicited during brain stimulation. Epileptic Disord 13: 435–440. CrossRef Medline

Gibson WS, Cho S, Abulseoud OA, Gorny KR, Felmlee JP, Welker KM, Klassen BT, Min HK, Lee KH (2017) The impact of mirth-inducing ventral striatal deep brain stimulation on functional and effective connectivity. Cereb Cortex 27: 2183–2194. CrossRef Medline

Lauterbach EC, Cummings JL, Kuppuswamy PS (2013) Toward a more precise, clinically-informed pathophysiology of pathological laughing and crying. Neurosci Biobehav Rev 37:1893–1916. CrossRef Medline

Manninen S, Tuominen L, Dunbar RI, Karjalainen T, Hirvonen J, Arponen E, Hari R, Jääskeläinen IP, Sams M, Nummenmaa L (2017) Social laughter triggers endogenous opioid release in humans. J Neurosci 37:6125–6131. CrossRef Medline

Morreall J (1987) The philosophy of laughter and humor. Albany NY: State University of New York.

Nummenmaa L, Tuominen L, Dunbar R, Hirvonen J, Manninen S, Arponen E, Machin A, Hari R, Jääskeläinen IP, Sams M (2016) Social touch modulates endogenous μ-opioid system activity in humans. Neuroimage 138: 242–247. CrossRef Medline

Olausson H, Lamarre Y, Backlund H, Morin C, Wallin BG, Starck G, Ekholm S, Strigo I, Worsley K, Vallbo AB, Bushnell MC (2002) Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci 5:900–904. CrossRef Medline

Petrovic P, Kalso E, Petersson KM, Ingvar M (2002) Placebo and opioid analgesia—imaging a shared neuronal network. Science 295: 1737–1740. CrossRef Medline

Provine RR (2000) Laughter: a scientific investigation. New York: Viking.

Saarimäki H, Gotsopoulos A, Jääskeläinen IP, Lampinen J, Vuilleumier P, Hari R, Sams M, Nummenmaa L (2016) Discrete neural signatures of basic emotions. Cereb Cortex 26: 2563–2573. CrossRef Medline

Scott SK, Lavan N, Chen S, McGettigan C (2014) The social life of laughter. Trends Cogn Sci 18:618–620. CrossRef Medline

Vogt BA (2005) Pain and emotion interactions in subregions of the cingulate gyrus. Nat Rev Neurosci 6:533–544. CrossRef Medline