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Emotional tears and NGF: a biographical appreciation and research beginning

ROBERT R. PROVINE

Department of Psychology, University of Maryland, Baltimore County, Baltimore, Maryland, USA

ABSTRACT

Emotional tearing is a potent, uniquely human, visual cue that shapes the perception of human facial expression, the tear effect. The role of tears in emotional signaling was demonstrated by contrasting the perceived sadness of human faces with tears against copies of those images that had the tears digitally removed. Remarkably, faces with tears removed seemed not only less sad but often of neutral emotional valence, showing such expressions as awe, concern, or puzzlement. Emotional tearing is a breakthrough in human sociality that resolves ambiguity and enhances the range and power of the face as a visual signaling medium. Emotional tears are a secondary consequence of lacrimal secretions originally evolved in the service of ocular maintenance and healing. Research from other labs has demonstrated that NGF (nerve growth factor) is elevated in tears and lacrimal glands after corneal injury, and that topical NGF promotes healing of corneal ulcers and may increase tear secretion in dry eye. It is suggested here that NGF and other growth factors may have a role in the evolution and development of the uniquely human capacity to produce emotional tears. The story about emotional tears is presented in the context of a reminiscence of the author's research mentorship with Rita Levi-Montalcini.

Key words

Levi-Montalcini • NGF • Tears • Emotion • Lacrimal gland

In September of 1965, I came to Washington University (St. Louis) as a psychology graduate student to study what later became known as neuroscience. The fledgling neuroscientist of that era had to be creative, fashioning a curriculum from a hodge-podge of courses in psychology, biology, engineering, neurology, and other offerings on the medical school campus. I looked for the best match between my interests and available resources and faculty. During my second year, I had the extraordinary good fortune to discover two individuals in the Department of Biology who were clearly on to something important, an impression validated later by the award of the National Medal of Science to one – Viktor Hamburger, and the Nobel Prize to the other – Rita Levi-Montalcini. From them I learned what matured into the discipline of developmental neuroscience. Celebrating the occasion of her 102nd year, I dedicate this essay to Rita Levi-Montalcini, focusing on lessons she taught me by word and deed about how to conduct a life in science.

Unlike Rita's career-long search for factors responsible for the birth, death, and survival of neurons, my research has been the interdisciplinary examination of the roots of human nature, from embryo to adult, adding pieces to the neurobehavioral puzzle as I follow the scientific trail from laughing (Provine, 2000) and yawning (Provine, 2005), to my recent foray into the origin of emotional tears (Provine et al., 2009) the present theme. Although I have made

Corresponding Author: Robert R. Provine, Department of Psychology, University of Maryland, Baltimore County, Baltimore, Maryland 21250, USA; Tel.: 410-455-2419 - Email: provine@umbc.edu

different decisions and followed a different career path than Rita, her influence remains.

My first formal meeting with Rita was as a student in Comparative Neuroanatomy, her only lecture course at Washington University. Although her class was fairly large, perhaps 75 or more students, it was fully booked, and her exams were of the essay type, which she personally graded and returned in a timely manner. Her lectures were entertaining and students acknowledged their appreciation at the semester's end with a standing ovation. Students knew that she was a famous scientist, and she played the part wonderfully. Her entrance to the lecture hall was preceded by an entourage of her white-coated Italian research associates and technicians who set up the projector and loaded her slides. Then, after an appropriate interval, Rita would enter – regal, smiling and gracious – and in a mild Italian accent, give a carefully crafted lecture in English.

After completing a dissertation which showed that spontaneous discharges in the spinal cord were responsible for embryonic behavior, I served several postdoctoral years as a Research Assistant Professor of Psychology and a Research Associate in the Departments of Biology and Ophthalmology at Washington University. During this postdoctoral period, Rita invited me to join her lab as an electrophysiologist and study the activity of tissue cultures of the developing insect nervous system. Working with Rita was an honor and opportunity, in part because it was obvious to me that she had at least a 50/50 chance of winning the Nobel Prize for her discovery of nerve growth factor (NGF). Thus began the exciting adventure of working with one of the most creative and interesting figures of 20th century biological science.

Rita had a definite theatric quality, even in the lab, but her drama was of a high scientific order and nicely complemented her research. Consider the NGF saga (Levi-Montalcini, 1988) that begins with Rita, a young Jewish physician in Fascist Italy, doing embryological research while hiding out from the villains Mussolini and Hitler. Every step of the NGF project was marked with the suspense, surprise, and resolution that makes for great drama and entertaining science, and aids the survival and proliferation of ideas in the scientific marketplace. Writers and professors seeking plot and human interest in their presentations love to tell the NGF story and incidentally contribute to the impact and lore of the research and its author. Rita's attire was also striking and elegant, consisting of tailored dresses, designer jewelry, patterned hose and high-heeled shoes, even when donning a lab coat.

Rita coupled her engaging personality with brilliance and an iron will. Those who praise her keen scientific intuition may overlook her formidable work ethic. I recall afternoon meetings with Rita in her office, where I reported on the day's progress. On these occasions, we were served espresso by her secretary – a nice touch, but there was always a tension associated with the demand to produce. I recall working days and nights, and usually half-days on weekends. Fortunately, there was an element of the chase – the pursuit of factors influencing nerve fiber outgrowth – that added an element of sport to the hard work.

Rita's legacy for me was the insight that science at the highest level could be pursued with modest resources, if complemented with tenacity and creativity. I also learned from Rita that good science makes a good story, with an interesting cast of characters, strong plot, development, and, hopefully, discovery and resolution. Few scientific adventures can aspire to the drama and significance of the NGF story, and there is only one Rita, but we can learn from its example as we tell our own, more modest tales. My most recent science story is about emotional tears, part of a larger story about life's neglected mysteries. Remarkably, by circuitous route, emotional tearing became part of the NGF story.

What's so interesting about tears? Tears bathe, lubricate, and heal the eyes, containing lysozyme, the body's own antibiotic (Frey, 1985; Lutz, 1999; Van Haeringen, 2001; Sullivan et al., 2002). Tears' contribution becomes obvious when they cease, producing the discomfort and pathology of "dry eye." Basal tears are continuously secreted by three sets of glands (the lacrimal gland and two others), to lubricate and wet the eye, and improve optical performance by smoothing the otherwise rough corneal surface. Tears form a multilayered film on the eye, an inner layer with lubricating mucin, a watery middle layer, and an oily outer layer that reduces evaporation and drying. Reflex tears triggered by irritation (e.g., onion, abrasion) and psychogenic (emotional) tears are primarily secretions of the lacrimal gland.

The secretion of tears from the lacrimal gland is controlled by complex, perhaps redundant, parasympathetic and sympathetic efferents (Van Haeringen, 2001). Parasympathetic innervation is via the pterygopalatine ganglion and sympathetic innervation via the superior cervical ganglion. Stimulation of the parasympathetic fibers increases tear secretion. Stimulation of sympathetic fibers may not directly increase tear secretion, but act indirectly through the blood supply of the lacrimal gland. Inputs from peptidergic fibers may also modulate lacrimal secretion. The uniquely human trait of emotional tears requires an additional cranial, extraocular source of lacrimal gland innervation.

The plot thickens when we examine psychogenic *emotional tearing*, the uniquely human secretion of tears by the lacrimal gland that has evolved into a visual signal of emotion. Emotional tears are a universally understood and uniquely human signal of sadness and other emotional states and acts, including crying, grief, despair, pain, happiness, anger, and empathy, as well as yawning, laughing, and sneezing. This is part of the bedrock of folk wisdom about our species. But do tears really signal sadness?

The scientific literature about crying and tearing revealed no test of this assumption. Published reports are full of interesting facts and findings about physiology, gender, personality, social context, culture, psychopathology, and health (Lutz, 1999; Vingerhoets and Cornelius, 2001). However, the large and energetic cadre of emotion researchers who study everything from face perception to psychophysiology somehow overlooked the problem of tears as signal.

My team of mostly undergraduate research students and I embarked on the examination of tears as a visual signal. The novelty of our problem brought excitement of the chase, but also the opportunity for error, not knowing what to expect, or how best to proceed. We started at what seemed to be the beginning.

The role of tears as a signal of sadness was examined by contrasting the perceived sadness of facial images with tears against copies of those images that had tears digitally removed with Adobe Photoshop (Provine et al., 2009). Two-hundred images of faces, 50 with tears, 50 with tears removed, and 100 tear-free control images, were presented sequentially as a sideshow, in counterbalanced order, on a computer monitor. Our 80 experimental participants had up to 5 seconds to rate each image on a 7-point Sadness Scale – 1 (*Not Sad At All*) to 7 (*Extremely Sad*) – before the next image appeared.

As expected, facial images with tears were rated as significantly sadder in appearance than the same images with tears removed. (Lacking Photoshop, the effect of tear removal can be approximated by using your finger to block-out tears in a photograph.) We term the ability of tears to make faces look sadder the *tear effect*. We confirmed the obvious, that *tears contribute to perceived sadness*. This necessary first step led to a serendipitous finding.

A startling but incidental discovery was that *tears resolve ambiguity of facial expression*. The removal of tears often produced faces of uncertain emotional valence, perhaps awe, concern, contemplation, fright or puzzlement, not simply of "less sadness". In other words, without tears, faces may not appear very sad, especially if they fall in the mid-range of the emotional spectrum. This is a more significant finding than it seems on first hearing. Emotional tearing taps an already present secretory process to add nuance and range to the limited neuromuscular instrument of facial expression, and contributes to the emergence of *Homo sapiens* as a social species. Tears are not merely a benign secretory correlate of sadness.

In the spirit of artist Roy Lichtenstein who produced many cartoons of crying girls, I offer a cartoon summary of the tear effect (Fig. 1). (The study used real halftone, color photos of people with and without tears, not cartoons.) The ability of simple cartoons to portray the effect is a measure of its robustness. Note how the tearful face in the left panel looks sadder than the adjacent image that is identical except that the tears were removed. If skeptical about our graphic manipulation, confirm it by using your finger to block out the tears in the left image.

My conclusion about tears as emotional stimuli received unanticipated confirmation from a student attendee at a Society for Neuroscience meeting where I first presented this study (Provine et al., 2009). She told me that a medical condition in previous years deprived her of both the ability to tear and to clearly express emotion. Absent teary eyes and cheeks, her friends and family could not comprehend her occasional bouts of sadness, and she was forced to explain her distress, with shaky voice, at times when it was most difficult. Her available cues of facial expression were often inadequate. She

Fig. 1. - When tears are removed digitally from images of crying faces, the resulting tearless faces appear not only less sad, but emotionally ambivalent, perhaps expressing awe, puzzlement or concern. Except for tears, the images in the left and right panel are identical. Tears add emotional meaning and nuance to the limited neuromuscular instrument of the face, the *tear effect*. This cartoon by Erin Ouslander illustrates the effect of tear removal, but was not an example of the color images of real people used in the study by Provine, Krosnowski and Brocato, 2009.

missed the automatic, potent, and informative signal of tears present before her illness. Her story was persuasive and prompted my planning for research about the effect of *dry eye* syndrome on emotional communication.

Individuals who have lost tearing through drug treatment, disease, or agenesis (Sullivan et al., 2002), provide a unique "experiment of nature" to test a basic issue about social behavior. Many people with dry eye probably share the experience of the student at the meeting. This problem remains open because it lies at the intersection of disciplines, escaping the notice of ophthalmologists who focus on the more immediate problems of tear production, replacement, and ocular pathology, not interpersonal communication.

Now that you are thinking about a life without tears, consider that you were born that way. Unlike vocal crying that is present at birth, emotional tearing does not appear until about 6-weeks later, probably when the efferent nerve supply to the lacrimal gland is established. Although this developmental lag has been known for many years (e.g., Darwin, 1872/1965), psychologists have not fully considered its implications. The emergence of tearing opens a new channel of visually mediated emotional communication between infant and caregiver. Tearing nicely complements vocal crying as a signal. Taken together, visual tearing and vocal crying provide the individual with a versatile, multisensory link with caregivers in childhood and companions in adulthood.

The tear effect has implications beyond tearing and vocal crying. Efforts to read the face have existed from antiquity and were a subject of Charles Darwin's classic *Expression of Emotions in Man and Animals* (1872/1965) and continued as a significant theme of Twentieth Century psychology, with Paul Ekman as a leading investigator. Ekman (Ekman et al., 1972), on the basis of decades of laboratory and cross cultural studies, proposed a group of *primary emotions* recognized by people of all races and cultures – happiness, anger, surprise, fear, disgust, and sadness – and developed detailed measures to describe these emotions and separate the "true" (spontaneous) from the "false" (faked). The details of this and competing stories are still being worked out, but the role of emotional tears is largely neglected. The tear effect demonstrates that the traditionally considered neuromuscular mechanism of facial behavior is not sufficient to portray the full range of emotional nuance.

Given that emotional tears are uniquely human and recently evolved, we may be witnessing an evolutionary process now in progress, when the intermediate steps are still visible, and before the lose-ends are tidied-up. This may explain tearing in such disparate acts as crying, sneezing, laughing and yawning. All may share unappreciated neurological

kinship as related emotions, near-emotions or protoemotions. Is the yawn a facial expression of the emotion of boredom or sleepiness? Is the laughing face an expression of happiness or exuberance? And what about the face during a sneeze that, in many ways, resembles that of the yawn or sexual climax? If my criteria for "emotion" seem nontraditional, consider that the official list of emotions is somewhat arbitrary, established by vote and sanctified by tradition.

Remarkably, the story of emotional tears takes me back full-circle to Rita's lab during my scientific youth during the early 1970s. As I was writing-up my preliminary study of emotional tears, I recalled that NGF is present in the salivary gland. Might NGF also be present in the lacrimal gland that produces tears? A search of the literature indicated that NGF is indeed present in the lacrimal gland (Nguyen et al., 1997) and the complex chemical soup of human tears (Park et al., 2008).

The presence of NGF in tears introduces intriguing medical and scientific issues. The concentration of NGF is elevated in tears, cornea and lacrimal glands after corneal wounding (Woo et al., 2005), suggesting that NGF plays a part in the healing process. Complementary evidence indicates that topical application of NGF promotes the healing of human corneal ulcers (Lambiase et al., 1998; Aloe et al., 2008) and may increase tear secretion in dry eye (Coassin et al., 2005; Muzi et al., 2010). Taken together, this evidence suggests that NGF is involved in ocular surface maintenance and corneal wound healing (Aloe et al., 2008). It follows that a deficit of NGF due to inadequate synthesis, release and/or utilization may cause a wide range of ocular pathology. No one has contrasted the NGF content and potential medicinal roles of basal tears and tears caused by emotions (e.g., sadness) and irritation (onion, abrasion), but these tear types differ in other aspects of chemical composition (Frey, 1985; Van Haeringen, 2001).

The visual signal of emotional tears is a secondary consequence of lacrimal secretions evolved in the service of ocular maintenance and healing. Nonemotional, healing tears may have originally signaled trauma to the eyes, eliciting care giving by tribe members or inhibiting physical aggression by adversaries. This primal signal may have later evolved through the process of "ritualization" into a sign of emotional as well as physical distress. This evolutionary scenario is reasonable but necessarily speculative.

The physiology and neurology of tear production is more concrete. NGF and other growth factors may provide insights into the evolution and development of emotional tears, a relatively modern and uniquely human response that is still being transformed, leaving fresh biological tracks. We can contrast the lacrimal processes of humans with related primates and mammals that produce basal and reflex tears, but not tears of emotion. The story of NGF and emotional tears is only beginning. Now that the behavioral phenomena of emotional tears have been described, the underlying physiological mechanisms can be pursued. A lesson of NGF research is that careful, step-by-step pursuit of the scientific trail can lead to serendipitous discoveries, both broad and deep. The study of normal and emotional tears may provide an exciting new chapter to the NGF story, this one about neurobehavioral development and evolution.

I will end as I started, with biographical musing. During a pilgrimage to Washington University a few years ago, I visited Rebstock Hall, the venerable Biology Building, and found oil portraits of Viktor Hambuger and Rita Levi-Montalcini, my two mentors, side-by-side, gazing down on the site of their scientific triumphs. This visit prompted a flood of memories. As I noted in the acknowledgments of my book *Laughter: A Scientific Investigation* (Provine, 2000), my gratitude to these very different mentors has not diminished. "I have intellectual debts to many teachers, students, and colleagues, but most of all to Viktor Hamburger and Rita Levi-Montalcini, who, many years ago, taught an embryonic graduate and postdoctoral student at Washington University about the ways of the developing nervous system and a life in science. They may not immediately recognize their influence, but it's there." Over the years and miles since our first encounter almost 45 years ago, I have always wondered, "what would Rita think," recalling that she was almost always right.

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