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Emotional proprioception: Treatment of depression with afferent facial feedback

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ABSTRACT

We develop the concept of *emotional proprioception*, whereby the muscles of facial expression play a central role in encoding and transmitting information to the brain's emotional circuitry, and describe its underlying neuroanatomy. We explore the role of facial expression in both reflecting and influencing depressed mood. The circuitry involved in this latter effect is a logical target for treatment with botulinum toxin, and we review the evidence in support of this strategy. Clinical trial data suggest that botulinum toxin is effective in treating depression. We discuss the clinical and theoretical implications of these data. This novel treatment approach is just one example of the potential importance of the cranial nerves in the treatment of depression.

1. Introduction

We and others have recently found that botulinum toxin A (BT) injected into the brow muscles has significant antidepressant effects as compared to placebo in randomized controlled studies (Wollmer et al., 2012; Finzi and Rosenthal, 2014; Magid et al., 2014). Although these findings may seem surprising at first glance, they might have been predicted by a line of thought going back over a century. While it is evident that our emotions influence our facial expressions, the reverse is less obvious. Yet Charles Darwin (Darwin, 1998) proposed this to be so over a century ago, and William James agreed (James, 1890).

Both of these scientists made special reference to this facial feedback effect, which we are calling *emotional proprioception*, in relation to depression. Darwin, for example, first observed the omega sign between the eyebrows, shaped like the last letter of the Greek alphabet (Ω) - a result of the corrugator muscles contracting and producing two vertical slits between the eyebrows, joined at the top by a horizontal crease. He recognized the omega sign as an indicator of melancholy and noted its disappearance when patients recovered. James famously stated that he did not cry because he was sad; rather, he was sad because he cried. In both instances the hypothesis was that the external representations of sorrow or grief were actually signaling back to the emotional centers of the brain, causing or exacerbating feelings of distress.

Over the ensuing decades experimental psychologists pursued what became known as the facial feedback hypothesis, and produced numerous results suggesting that Darwin and James were correct. Signaling between the emotional centers of the brain and the facial muscles is bidirectional (Adelmann and Zajonc, 1989; Niedenthal, 2007). The goals of this article are: 1. To develop the concept of *emotional proprioception* (EP) and describe its underlying neuroanatomy; 2. To show how modulating EP can be beneficial in treating depression and perhaps other distressed states; and 3. To suggest that such interventions may be regarded as just one of several ways in which influencing cranial nerve function may have antidepressant effects.

2. Facial feedback hypothesis

It took about a century after Darwin's seminal observations for researchers to systematically investigate what happens to emotional states in the brain when, either consciously, or unconsciously, the musculature of facial expression is activated.

Early research revealed that people rated cartoons as funnier when smiling than when frowning (Cupchik and Leventhal, 1974). Likewise, people also rated negative imagery as more aggressive when frowning, than when smiling (Laird, 1974). Critics of these early experiments observed that participants were aware that their facial expressions were happy or sad which might have biased the

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results. To try and eliminate such bias, subsequent researchers provided a good cover story for the experiment so that subjects were unaware of its real purpose. Instead of asking subjects to adopt a specific expression, they asked them to perform discrete facial actions, apparently unrelated to emotional expressions. For example, researchers asked subjects to hold a pen between their lips, (to inhibit smiling) or between their teeth (to facilitate it) (Strack et al., 1988). Subjects then rated the funniness of cartoons. Smiling subjects found the cartoons funnier than those prevented from smiling. Thus the simple contraction of the zygomaticus muscle, such as occurs when we smile, gives a positive spin to decision making.

Likewise, experiments have shown that attaching golf tees to both sides of the forehead, and asking people to use their facial muscles to bring the tees closer together, causes people to rate unpleasant photographs more negatively (Larsen et al., 1992). Frowning, regardless of why, causes a more negative evaluation of an emotional image and influences decision making.

Numerous researchers have reached similar conclusions using different methods to manipulate facial expressions. For example, one group utilized the fact that pronouncing certain vowels causes contraction of different sets of facial muscles (Adelmann and Zajonc, 1989). For example, the inclusion of the German vowel *u* in a word will prevent its speaker from smiling, while, at the same time, help create a frown. In one study, native German speakers were asked to read two stories aloud. Each story was equivalent in emotional tone and semantic content, but one story contained many words containing the u vowel, while the other contained no u words. The subjects were then asked to rate the stories on many parameters including which one they liked better. Their participants liked the no-u stories better, suggesting that frowning negatively influences emotion based decision-making.

To investigate how facial expressions affect the autonomic nervous system (ANS), Ekman and colleagues asked their subjects to contract precise sets of facial muscles, creating expressions of surprise, fear, disgust, anger, happiness and disgust, or to recall an experience that elicited these emotions (Ekman et al., 1983). Objective measures of the ANS -heart rate, blood pressure, skin conductance, sweating – were altered more by contracting facial muscles than by the recall of an emotional memory.

In summary, converging lines of evidence suggest an important effect of the facial muscles on mood: specifically, the zygomaticus muscles involved in smiling promote happy mood, and the corrugator muscles involved in frowning promote gloomy mood.

3. Emotional proprioception

Afferent nerve fibers appear to relay emotional information to the brain on a moment to moment basis, signaling our emotional state.

We propose that the brain utilizes facial muscle expression to provide such *emotional proprioception* (Finzi, 2013a). When we paralyze muscle fibers with BT this may signal to trigeminal nerve endings- possibly those involved in registering pain, position and muscle tension- a relief of physical stress, resulting in decreased emotional stress.

A link between corrugator muscle activity and amygdala activation has been observed (Heller et al., 2014; Lee et al., 2012). Brain FMRI data and EMG recordings of the corrugator muscle were simultaneously acquired in subjects who viewed emotionally negative or neutral images. Negative-picture viewing induced increases in corrugator activity along with increases in amygdala activation. Increased corrugator activity was also associated with deactivation of the ventromedial PFC.

Depressed patients who experience a remission induced either by paroxetine, or by cognitive behavioral therapy, show reduced amygdala overactivity (DeRubeis, 2008; Ruhé et al., 2012).

4. Evidence for antidepressant effects of botulinum toxin A

In an initial case series, one of us (EF) injected BT into the frown of ten depressed patients, eight of whom went into remission after one treatment (Finzi and Wasserman, 2006; Finzi, 2013b). The study was limited by its small size, lack of controls, and lack of blinding. In three subsequent randomized, double blind and placebo controlled trials, we and other researchers have found response rates of 50–60% in major depression, with about one-third of patients going into remission (Wollmer et al., 2012; Finzi and Rosenthal, 2014; Magid et al., 2014, 2015) (Table 1). BT showed antidepressant effects both when used as an ancillary treatment and by itself.

How might injecting BT into the corrugator muscle influence the emotional brain?

FMRI imaging has shown that subjects who received BT injections into their frown muscles had amygdala that were less responsive to negative stimuli (Hennenlotter et al., 2009). Recent work has confirmed that amygdala activity in response to angry faces was decreased when the frown muscles were paralyzed by BT injection. Furthermore, amygdala activity returned to its original inducible state after the effects of the BT injection had worn off, confirming that BT reversibly severed afferent feedback from the

Table 1
Clinical trials using botulinum toxin to treat depression.

Study	Design	Patients taking antidepressants	N	Results
Finzi and Wasserman, 2006	Open label trial 10 depressed females	5/10	10	BT remission of depressive symptoms in 8 of 10 patients.
Wollmer et al., 2012	RCT 15 placebo 15 BT	29/30	30	BT > placebo when given as adjunctive treatment. 60% vs 13% response rare ($p = 0.02$) 33% vs 13% remission rate (N.S.)
Finzi and Rosenthal, 2014	RCT 41 placebo 33 BT	31/74	74	BT > placebo both as adjunctive and solo treatment. 61% vs 12% response rate ($p < 0.0001$) 48% vs 12% remission rate ($p < 0.001$)
Hexsel et al., 2013	Open label trial 25 depressed patients	25/25	25	Depressed patients had a 54% decrease in BDI scores ($p < 0.001$). Self esteem scores also significantly improved.
Magid et al., 2014	Crossover RCT 19 placebo 11 BT	26/30	30	Depressed patients continued to improve beyond duration of cosmetic effects. 45% vs 5% response rate ($p = 0.007$) 33% vs 5% remission (N.S.)

corrugator muscle to the amygdala (Kim et al., 2014).

Thus, understanding the influence of EP on mood regulation has led us to a potentially valuable new antidepressant approach – BT as an antidepressant. This approach is especially appealing insofar as facially injected BT has very few side effects, virtually no described interactions with systemically administered drugs, and can be used as a stand-alone therapy or adjunctive to concomitant antidepressant medications.

5. Possible underlying neuroanatomical circuitry involved in botulinum toxin antidepressant effect

In order to understand the EP pathway that may be at work in this antidepressant effect it is worth noting that muscular activity in the region of the brow influences proprioceptive fibers of the optic branch of the trigeminal nerve. This in turn may activate the ventromedial PFC via the mesencephalic trigeminal nucleus and locus ceruleus, the latter of which has direct connections with both the amygdala and the PFC (Matsuo et al., 2015) – structures critical for emotional regulation.

We hypothesize that by injecting BT into the brow, thereby temporarily and reversibly paralyzing corrugator muscle, we influence the proprioceptive signal sent along the optic branch of the trigeminal nerve. Thus at a neuroanatomical level BT is literally relieving the pain and stress carried by the corrugator muscles of the brow, supporting a theory first proposed by Darwin about 150 years ago.

6. Further implications

The concept of EP as a target for therapeutic intervention leads to two lines of speculation as to how else we might be to help able patients suffering from emotional disorders. First, what other emotional conditions might benefit from intervention with BT? And second, might the influence of this one particular cranial nerve, the trigeminal, be just one example of therapeutic benefits of modifying cranial nerve functions? Let us deal with each of these ideas in turn.

First, expressions of distress such as frowns or grimaces are by no means unique to depression. They are common to all situations that involve grief, panic, fear and anger—emotions that might be present for example in people with anxiety disorders and anger management problems. A logical extension of our work, therefore, would be to consider the use of BT for these and other conditions.

Second, the cranial nerves might be valuable conduits for therapeutic exploration. Several interventions that influence cranial nerves have already been shown to have antidepressant effects. Thus, light therapy (optic nerve) benefits both seasonal and non-seasonal depression (Lam et al., 2016). Fragrances (olfactory nerve) may elevate mood (Perry and Perry, 2006). Vagal nerve stimulation has been used in refractory depression with beneficial effects (Cristancho et al., 2011). And music has long been appreciated for its soothing and antidepressant effects (Raglio et al., 2015). Further exploration of cranial nerve manipulation in psychiatry appears warranted.

7. Conclusions

In summary, EP is a useful concept for understanding the influence that facial muscles have on the emotional centers of the brain. We suggest that BT may be considered a potential Rx for depression. As more data accumulate, we will learn when and how best to deploy this new tool.

These studies of BT in depression also provide new horizons for other uses of this protein, and might stimulate us to give further consideration to the antidepressant uses of the cranial nerves.

Conflict of interest

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