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Review

Toward a more precise, clinically—informed pathophysiology of pathological laughing and crying

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ABSTRACT

Involuntary emotional expression disorder (IEED) includes the syndromes of pathological laughing and crying (PLC) and emotional lability (EL). Review of the lesion, epilepsy, and brain stimulation literature leads to an updated pathophysiology of IEED. A volitional system involving frontoparietal (primary motor, premotor, supplementary motor, posterior insular, dorsal anterior cingulate gyrus (ACG), primary sensory and related parietal) corticopontine projections inhibits an emotionally–controlled system involving frontotemporal (orbitofrontal, ventral ACG, anterior insular, inferior temporal, and parahippocampal) projections targeting the amygdala–hypothalamus–periaqueductal gray (PAG)–dorsal tegmentum (dTg) complex that regulates emotional displays. PAG activity is regulated by glutamatergic NMDA, muscarinic M1-3, GABA-A, dopamine D2, norepinephrine alpha-1,2, serotonin 5HT1a, 5HT1b/d, and sigma-1 receptors, with an acetylcholine/GABA balance mediating volitional inhibition of the PAG. Lesions of the volitional corticopontine projections (or of their feedback or processing circuits) can produce PLC. Direct activation of the emotional pathway can result in EL and the laughing or crying of gelastic and dacrystic epilepsy. A criterion-based nosology of PLC and EL subtypes is offered.

Contents

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1. Introduction

Syndromes of involuntary laughing and crying have long been recognized. Darwin is thought to have offered their first description in 1872 (Darwin, 1872). Oppenheim and Siemerling (1886) described exaggerated emotional behavior associated with lesions of tracts descending to the brainstem. Oppenheim first used the term *pseudobulbar affect* (PBA) to describe "spasmodic explosive bursts of laughter or weeping" and linked the condition to posterior frontal subcortical white matter, the internal capsule, and basal ganglia lesions (Oppenheim, 1911). PBA is classically associated with pseudobulbar palsy (Langworthy and Hesser, 1940) although some have used the term to encompass the syndromes of *pathological laughing and crying* (PLC) and *emotional lability* (EL) (Miller et al., 2011). Wilson first described PLC as uncontrollable emotional displays disproportionate to their evoking stimuli, dissociated from mood, and stereotyped in response (Wilson, 1924), and described a "voluntary" inhibitory system acting on brainstem centers that was first conceived of by Oppenheim (1911). Poeck subsequently proposed PLC diagnostic criteria, including evocation by non-specific stimuli, mood-independence, and involuntary nature, in contrast to EL, which was stimulus-appropriate, mood-congruent, variable (not stereotyped), and distractible, though not volitionally suppressible (Poeck, 1969). More recently, Cummings et al. (2006) detailed diagnostic criteria for *involuntary emotional expression disorder* (IEED), inclusive of PLC and EL subsyndromes. Parvizi et al. (2009) have provided a detailed history of the condition.

Key features of PLC across the various nosologies (Wilson, 1924; Poeck, 1969; Cummings et al., 2006), then, include stereotyped episodes of involuntary laughing and/or crying that are inappropriate or disportionate to the inciting stimulus and occur independent of underlying mood. PLC may be distinguished from EL, which includes variable (non-stereotyped) episodes of involuntary laughing and/or crying that are consistent with, though disproportionate to, the stimulus and are congruent with mood. IEED occurs in a variety of neurological disorders (Schiffer and Pope, 2005; Wortzel et al., 2008; Parvizi et al., 2009), as listed in Table 1. More recently, PLC has been described in association with startle and immediately preceding the onset of akinetic mutism in 3 patients with Creutzfeldt-Jakob disease prion protein gene V180I mutations (Iwasaki, 2012).

The epidemiology of IEED (Table 2) has been confounded by varying nomenclatures (Feinstein et al., 1997; Wortzel et al., 2008), including terms such as affective lability, emotionalism, emotional dyscontrol, emotional incontinence, EL, excessive emotionality, forced laughter or crying, inappropriate hilarity, pathological affect, pathologic emotionality, pathological emotionalism, pathological weeping, and pseudobulbar crying (Arciniegas et al., 2005; Cummings et al., 2006). We use the well-defined terms IEED, including PLC and EL, reserving PBA for cases attended by features of pseudobulbar palsy, as detailed above. A wide variety of treatments have been employed to treat these related conditions, including levodopa, antidepressants, glutamatergic agents, the dextromethorphan-quinidine combination approved by the US Food and Drug Administration (FDA) for PBA, and other classes of drugs (Wortzel et al., 2008; Pioro, 2011).

Table 1
Distinguishing features of PLC and EL.

	PLC	EL
IEED feature		
Involuntary	Yes	Yes
Uncontrollable	Yes	Yes
Sudden	Yes	Often
Excessive	Yes	Often
Exaggerated expression	Yes	Yes
Inappropriate response	Yes	Yes
Consistent with mood	Can be	Usually
Multiple episodes	Yes	Yes
Change from baseline	Yes	Often (if not congenital)
Significant distress	Usually	Depends on insight
Social/occupational dysfunction	Often	Often
Distinguishing subtype features		
Stereotyped response	Yes	No (variable)
Stimulus-inappropriate	Yes	No
Mood-independent	Yes	No

The purpose of this article is to provide a synopsis of the literature relevant to understanding PLC pathophysiology. In light of the phenomenological characteristics of PLC and EL, PLC would appear to involve the disinhibition, or release, of the affective relexes of laughing and crying whereas EL comprises a more complex dysmodulation of mood and its affective expression. PLC and EL likely have overlapping yet distinct pathophysiologies. We will consider the evidence for the emotional and volitional systems pertinent to IEED, the phenomena of emotional and volitional facial paresis (EFP and VFP), animal studies of neural structures implicated in emotional expression, the clinical literature of emotional expression, the connectivity (hodology) of involved structures, and neuropharmacological aspects of treatment.

2. Volitional and emotional neural pathways in emotional expression

A variety of structures have been put forth as controlling emotional expression. The most compelling and time–tested concept is that of Wilson (1924), who championed the view of an emotionally-driven "involuntary" pathway that is inhibited by a consciously-driven "voluntary" pathway. Lesions in the volitional motor pathways would produce a disinhibition of emotional motor pathways, producing PLC. While the volitional pathway is

Table 2
IEED prevalence in neurological diseases.

Neurodegenerative disease	
Amyotrophic lateral sclerosis	49%
Alzheimer's disease	18–74%
Multiple system atrophy–cerebellar type	36%
Parkinson's disease	4–6%
Cerebrovascular disease	11–34%
Multiple sclerosis	10%
Traumatic brain injury	5–11%