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# Can premorbid episodes of diminished vagal tone be detected via histological markers in patients with PTSD?

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**Abstract**

While laboratory methods for estimating genetic susceptibility for adult psychopathology have received much recent attention, laboratory methods for objectively estimating a person's early autonomic nervous system perturbations have been under-researched. Research on heart rate variability suggests that early life episodes of diminished vagal tone may predict poor stress resilience in adults. This article will detail a research method for retrospectively estimating in adults the chronology of diminished vagal tone episodes experienced prior to age 10. This method makes use of the developing enamel matrix, one of very few tissues that cannot recover after being stressed.


*Keywords:* Acute stress reaction; Parasympathetic nervous system; Gulf war syndrome; Nucleus ambiguus; Dental enamel hypoplasia (DEH)

## 1. Introduction

> 'We need research designed to develop better measures of the environment...' and to 'examine the nature of vulnerability/stress interaction, with stress conceptualized broadly…' Davidson, RJ et al. 2002. Neural and Behavioral Substrates of Mood and Mood Regulation. Workgroup report for the NIMH strategic plan for mood disorders research. Biological Psychiatry, 52, 478–502

A new technique for detecting premorbid episodes of diminished vagal tone and their approximate chronology that the author describes here fits especially well with the above recommendation for NIMH research priorities. This technique also complements the extensive and important research on heart rate variability in human stress disorders (e.g. Cohen et al., 2003). This line of research also fits well with Porges' Poly-Vagal hypotheses of stress emphasizing the upper (limbic) branches of the vagus and tying together the facial, oral-buccal, laryngeal, and cardiac component of the acute stress reaction.

## 2. The parasympathetic nervous system in acute stress

Extreme autonomic nervous system perturba-

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tions during early life can produce long-term deleterious effects. For reviews of recent important contributions, see work by Porges et al. (Porges, 2001; Sahar et al., 2001b), McEwen (McEwen and Lasley, 2002; Seeman et al., 2001; Goldstein and McEwen, 2002) and Sapolsky (Sapolsky, 2002, 1997).

Stress research has long focused on the adverse effects of adreno-cortical activation. More recently, following Porges' important theoretical contributions, there has been attention to diminished vagal tone as an important final common pathway leading to the adverse effects of acute stress reaction (Porges, 2001; Sahar et al., 2001b).

The vagus is a complex bi-directional system with a left and right myelinated branch. Each branch has two source nuclei with fibers originating either in the nucleus ambiguus or in the dorsal motor nucleus. As Porges (1995) points out, while previous research has focused on the dorsal motor nucleus of the vagus, little attention has been given to the motor pathways originating from the vagal nucleus ambiguus.

The nucleus ambiguus is the more anterior and rostral (limbic) of the two vagal nuclei. Furthermore, a potentially important hemispheric lateralization exists in the ambiguus motor neurons. As articulated by Porges (1995), p. 228):

> 'In the study of acute stress and emotional expression, vagal pathways originating in the right nucleus ambiguus are critical. The right nucleus ambiguus provides the primary vagal input to the sino-atrial node to regulate heart rate and to the larynx to regulate the vocal intonation. Acute stress, especially during painful procedures, is associated with high heart rate and high pitch vocalizations and cries. Both characteristics are determined by a withdrawal of vagal efferent outflow originating in the nucleus ambiguus. These vagal efferents can act instantaneously to change heart rate and the pitch of vocalizations. Unlike the involuntary and often prolonged characteristic pattern of vagal outflow from the dorsal motor nucleus, the outflow from the nucleus ambiguus may exhibit rapid and transitory patterns associated with perceptive pain or unpleasantness. The central nucleus of the amygdala, implicated in emotional lability [and fear], directly communicates with the nucleus ambiguus. Thus, the branch of the vagus originating in the nucleus ambiguus is closely linked to the rapid expression and regulation of emotional state.'

## 3. Nucleus ambiguus control of enamel secretion by ameloblasts

Research on heart-rate variability has implicated the nucleus ambiguus in both Acute Stress Reaction and Combat Related-Posttraumatic Stress Disorder (CR-PTSD) (Sahar et al., 2001a; Porges, 1995). There has been little attention given to the fact that vagal cholinergic neurons originating in the nucleus ambiguus control the trophic parasympathetic regulation of blood flow to the enamel secreting ameloblasts. The nucleus ambiguus pathway ending in the ameloblast layer travels by a circuitous route through other cranial nerves (Harati and Machkhas, 1997; Nieuwenhuys et al., 1981). The dramatic slowing of enamel secretion by the ameloblast is produced by an abrupt drop in nucleus ambiguous cholinergic firing (rostral vagal tone), which also produces change in vocal intonation, facial expression, and especially saliva secretion and thus the symptom of xerostomia. All of these are well-documented physical signs of acute stress reaction. These neurons affecting the rate of enamel secretion are of the same extended amygdala origin as the neurons that coordinate increased heart rate, breathing, and peri-laryngial constriction (high-pitch vocalizations and the feeling of a 'lump in the throat') which are part of acute stress reaction (Porges, 1995).

As a rule, during acute stress reaction, the trophic parasympathetic functions slow or cease transiently (Fagius, 1997). Prior to age 10, the trophic parasympathetic 'luxury' functions that typically slow or cease during stress include secretion of the still developing dental enamel matrix (Goodman and Rose, 1990; Skinner and Anderson, 1991; Hillson, 1996).

## 4. 'DDE-SH RINGS': a proposed technique for estimating early vagal tone chronology

This technique uses some of the histological markers known in paleopathology as developmental defects of enamel or DDE (Larsen, 1999; Roberts and Manchester, 1997; Ash, 1993; Murray et al., 1987).

In this review, the term DDE-stress histomarker rings (DDE-SH Rings; pronounced 'desh rings')

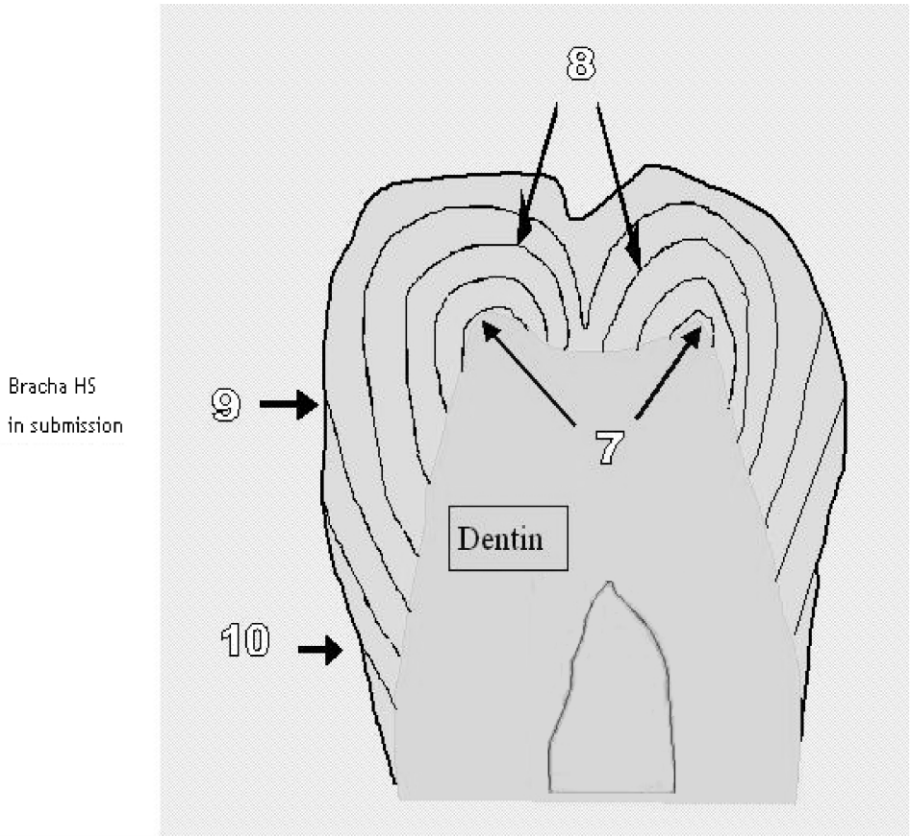


Fig. 1. An idealized drawing of DDE-SH Ring (slowing of enamel growth) in a third molar of a hypothetical adult who experienced acute episodes of diminished vagal tone lasting 10–20 days every 6 month between ages seven and ten.

is used primarily to differentiate them from other DDE, which are mineralization defects. The term was chosen to also emphasize the recent understanding of the etiology of this particular subset of dental histomarkers. DDE-SH Rings have been developed as a histomarker based upon extensive carefully conducted research by paleopathologists, forensic dental anthropologists, and bio-archeologists. For recent work, see Dean, Leakey, and Reid (Nature 2001). See Fig. 1 for an idealized drawing of DDE-SH Rings in a hypothetical patient.

DDE-SH Rings are dome-shaped malformations demarcating the layer of dental enamel secreted by ameloblast cells during periods associated with diminished vagal tone (Aufderheide and Rodriguez-Martin, 1998). Both acute and sub-chronic stress can be estimated via DDE-SH Rings of various widths.

There are various grades of histological features which together are called DDE-SH Rings. These include microscopic histomarkers (Circadian Cross Striations, Circaseptan Striae of Retzius, Accentuated Striae of Retzius, and Wilson Bands) as well as clinically detectable histomarkers (Linear Enamel Hypoplasias and other Gross Enamel Hypoplasias) (Guatelli-Steinberg, 2001; FitzGerald, 1998; FitzGerald and Rose, 2000). There is growing consensus in the paleopathology and dental anthropology literature that 'Selyean stress' lasting 1-week or longer will produce DDE-SH Rings (Aufderheide and Rodriguez-Martin, 1998; Hillson, 1996) and that the transient disruption of

ameloblast activity during diminished vagal tone can be detected as long as the tooth remains largely intact (Liebgott, 2001; FitzGerald and Rose, 2000). Studies suggest that the DDE-SH Rings called Accentuated Striae of Retzius, may be especially useful and can be produced in as little as 1 or 2 days of extreme stress (Wright, 1990).

At present, it may be too early to determine which histomarker will be the most useful in clinical stress research in humans. Nevertheless, based on the above literature and additional literature cited below, we have proposed that human enamel is an untapped resource for detecting periods of diminished vagal tone that occur during early brain development (Bracha et al., 2003b,a, 2002).

DDE-SH Rings are conceptually akin to tree rings that mark periods of environmental adversity during a tree's development. The developing enamel matrix is one of very few tissues that cannot recover after being stressed (Dean et al., 2001; Reid et al., 1998; Reid and Dean, 2000b; Antoine et al., 1999; Dean, 2000; Hillson, 1996; White, 1991; Risnes, 1998; Risnes et al., 1996; Simpson, 1999; Dean, 1999; Reid and Dean, 2000b,a). Thus, the developing enamel has promise as an accessible repository of information on vagal tone chronology prior to age 10 when human third molars (the last developing teeth) complete crown formation (Goodman and Rose, 1990; Skinner and Anderson, 1991).

We propose that as one of the very few potential markers of premorbid physiologically relevant stress, DDE-SH Rings may be important for research on the etiology of anxiety and mood disorders. DDE-SH Rings may be useful in researching disorders such as CR-PTSD, chronic fatigue syndrome (CFS), and fibromyalgia syndrome (FS). Additionally, DDE-SH Rings may be useful in researching medically unexplained syndromes, such as Gulf War Veterans' Illnesses (GWVI), in which it is hard to determine whether pre-enlistment stress sensitization has an etiological role in the patient's current illness. The vagus-mediated mechanism underlying these histological defects have not previously been fully articulated.

## 5. Current clinical and forensic uses

Earlier DDE-SH Rings research in contemporary populations has been conducted by pediatric dentists and focused almost entirely on deciduous dentition. DDE-SH Rings in deciduous teeth were found to be useful tools for ruling in, or ruling out, late prenatal, intranatal, and infancy distress in research participants (Leviton et al., 1994; Levine et al., 1979).

Early studies of DDE-SH Rings conducted with deciduous teeth suggest that clinical DDE-SH Rings may be several times more common in patients with neurodevelopmental disorders than in controls. This is consistent with the role that diminished vagal tone during infancy, intranatal and prenatal periods play in the etiology of neurodevelopmental disorders (Via and Churchill, 1957; Cohen and Diner, 1970). Additionally, poorer clinical outcomes were shown to be associated with DDE-SH Rings (Murray et al., 1987). Early stressors, as estimated by the location of DDE-SH Rings, were associated with a more severe impairment (Murray et al., 1987). These studies lend support to the potential utility of DDE-SH Rings in permanent dentition.

Forensic investigators (Skinner and Anderson, 1991) reported in detail the pattern and timing of a series of DDE-SH rings. They demonstrated that the rings could be matched to a premortem clinical record of experienced physiological stress. This chronological determination is possible since the rate of enamel elongation is well known. Prior studies observed that, although there is a certain amount of known non-linearity in this rate, permanent enamel elongates in the cervical (root) direction at approximately 2.60 μm/day (approx. 1 mm/year). This information was obtained by measuring the mean inter-striae distance for a first permanent molar from a terminally ill child given timed injections of tetracycline, which marked the enamel with orange striae (Massler et al., 1941).

## 6. Prevalence of DDE-SH RINGS in molars in non-clinical populations

Our current research specifically focuses on DDE-SH Rings in permanent molars. Permanent

molars have been the least studied human teeth in the investigation of vagal tone. The most severe form of DDE-SH Rings (Enamel Hypoplasias) is relatively uncommon in permanent molars (Suckling et al., 1976; Murray and Shaw, 1979). A review of five large studies of contemporary populations (over 1000 subjects), concluded that approximately 11% of first molars and 5% of second molars show enamel hypoplasias (Goodman and Rose, 1990). The prevalence in third molars is unknown. The one published study of 24 healthy subjects over age 16 (Sarnat and Schour, 1941) reported enamel hypoplasias in none of the third molars.

The prevalence of less severe (subclinical) DDE-SH Rings is also unclear, although generally believed to be higher. Wright found that out of 43 permanent teeth with subclinical DDE-SH Rings, only 51% manifested clinical hypoplasias (Wright, 1990). The first study of subclinical DDE-SH Rings specifically focusing on molars from clinical research participants ($N=300$) is currently being completed by our research team.

## 7. Evolutionary reasoning for research on DDE-SH Rings

A clinical research program investigating enamel markers of premorbid vagal tone perturbations is a step towards developing a clinical tool (biomarker) for researching the autonomic nervous system's response before, during, and after acute stress reaction. Evolutionary biological reasoning has led us to take this approach. Extensive research suggests that survival during extreme stress, throughout human evolution, depended primarily on blood supply to the brain and heart. Several other organs, such as skin, intestines, other mucousae, nails, hair, and bone were of lower priority and grow predominantly during spans of low stress such as sleep (Appenzeller, 1990). We have reasoned that the anatomical structures of lowest survival priority may be a neglected indicator to the negative effects of stress. While little research has been done on the topic, amelogenesis of the still erupting teeth is one luxury trophic function likely to be among the lowest survival priorities during extreme stress.

## 8. Few biological markers are unaffected by adulthood stress

One unique strength of our DDE-SH Rings technique for estimating premorbid vagal tone chronology is that enamel cannot naturally remodel or undergo repair after its initial formation in the way that other human tissues, including dentin, bone, and brain tissue can (Goodman and Rose, 1990; Skinner and Anderson, 1991; Hillson, 1996; Rose et al., 1978). DDE-SH Rings, therefore, cannot be affected by a stress reaction that occurs after the age at which enamel secretion ceases (shortly after age 10 in humans). Since enamel has the permanence of stone, DDE-SH Rings are indelible indicators of pre-pubertal autonomic perturbations. In other words, DDE-SH Rings are a specific marker of infancy and childhood stress and are completely unaffected by post-pubertal and adult stress. Specifically, DDE-SH Rings cannot be produced by research confounding factors after age 10 such as current or recent exposure to alcohol, drug abuse, smoking, medical illness, medications, poor nutrition, or head injuries. Similarly, DDE-SH Rings are not affected by the research participants' quality of self-report as influenced by current mood, cooperativeness, or cultural factors.

## 9. Conclusion

This new technique for estimating vagal tone chronology during early brain development that we describe here, fits especially well with the most recent recommendation for NIMH research priorities. An indelible histological marker that can retrospectively estimate vagal tone chronology during the first 10 years of life would be valuable for clinical research on acute stress reaction, acute stress disorder and on PTSD. The possible role of stress sensitization and kindling-like mechanisms in the etiology of anxiety and mood disorders points to an even wider range of disorders to which this technique may be applicable (Essex et al., 2002; Sax and Strakowski, 2001; Bell et al., 1996; Post et al., 1995; Stam et al., 2000). Additionally, it may be valuable for other disorders of

unclear etiology such as CFS, FS, multiple chemical sensitivity syndrome, and GWVI.

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