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PERSPECTIVES

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The human fear-circuitry and fear-induced fainting in healthy individuals

The paleolithic-threat hypothesis

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Abstract The Paleolithic-Threat hypothesis reviewed here posits that habitual efferent fainting can be traced back to fear-induced allelic polymorphisms that were selected into some genomes of anatomically, mitochondrially, and neurally modern humans (*Homo sapiens sapiens*) in the Mid-Paleolithic because of the survival advantage they conferred during periods of inescapable threat. We posit that during Mid-Paleolithic warfare an encounter with "a stranger holding a sharp object" was consistently associated with threat to life. A heritable hard-wired or firm-wired (prepotentiated) predisposition to abruptly increase vagal tone and collapse flaccidly rather than freeze or attempt to flee or fight in response to an approaching sharp object, a minor injury, or the sight of blood, may have evolved as an alternative stress-induced fear-circuitry response. Such a stable (balanced) polymorphism for the hemodynamically "paradoxical" *flaccid-immobility* in response to these stimuli may have increased some non-combatants' chances of survival. This is consistent with the unusual age and sex pattern of fear-induced fainting. The Paleolithic-Threat hypothesis also predicts a link to various hypo-androgenic states (e.g. low dehydroxy-epiandrosterone-sulfate. We offer five predictions testable via epidemiological, clinical, and ethological/primatological methods. The Paleolithic-Threat hypothesis has implications for research in the aftermath of man-made disasters, such as terrorism against civilians, a traumatic event in which this hypothesis predicts epidemics of fear-induced fainting.

Key words fainting · human evolution · war · combat · fear-circuitry · androgens · stress-induced disorders

Background

Fainting in the elderly is hemodynamically well understood [11]. However, habitual fainting in healthy, young individuals is difficult to explain hemodynamically. For example, such patients may faint even while in the sitting or supine positions [19]. While habitual fainting is also observed in adult males, even active duty military personnel, it has been widely observed that the prevalence of fear-induced fainting dramatically drops following puberty in males but not in females. However, there are no adequately designed studies that have examined this observation [19].

One role of perspective articles is to look at conventional wisdom from a new angle, often from the viewpoint of a different scientific discipline, and present a hypothesis. Hypotheses are by definition conjectural. However, hypotheses encourage testing of their predictions in future studies or in existing databases. In this ar-

ticle we will propose testable predictions based on possible distal neuroevolutionary etiology ("why") [5, 7, 9, 10, 12, 16, 17], which can be complementary to the neuro-cardiological research on proximal physiological etiology ("how") [1, 18].

Anatomically and mitochondrially modern humans (archaic *Homo sapiens*) evolved in East Africa into *neurally* modern humans (*Homo sapiens sapiens*) approximately between 200,000 and 60,000 years ago, during the Mid-Paleolithic [10, 12, 13, 16]. Research on Mid-Paleolithic evolutionary pressures and lifestyles was instrumental in guiding recent research on mitochondrial disorders, degenerative disorders, and especially obesity [9, 16]. For Paleolithic foragers (hunters, fishers, gatherers), storing calories as body fat made calories portable, invulnerable to spoilage or theft (and able to last through long periods of famine). Furthermore, studies of skeletal remains find that calcium intake in the Mid-Paleolithic came mostly from crushed animal ribs and vertebrae, not milk [10]. Finally, the first scientific method to document the diet of mitochondrially modern humans, which was high in fiber and proteins and low in carbohydrates, were obscure paleo-anthropological methods such as the study of fossilized excrement (coprolites) [10].

The Paleolithic-Threat hypothesis is similarly based on little-known paleo-anthropological research. It posits that some medically-unexplained habitual fear-induced fainting is related to evolutionary pressures during the Mid-Paleolithic era of evolutionary adaptedness.

Fear-induced fainting: relevant recent findings

We use the term "fear-induced fainting" to refer to the spectrum of conditions, ranging from malignant efferent vasovagal syncope to mild habitual faintness and "swooning". The prevalence of fear-induced fainting is unclear. A comprehensive methodological review [19] concludes that there are no adequate studies of its prevalence and that the available studies cannot be compared since they have used varying definitions. Estimates of overall prevalence range from 5 %–15 % [19].

Furthermore, although the decrease of fear-induced fainting with age is widely observed, no studies have adequately examined the prevalence of this age-related change [19]. In a review of older studies, "blood-injury fears" were reported in 5 % of adults and in 27 % of nine- to twelve-year olds. The sex of the subjects was unspecified [19]. Similarly, data cited by Newton et al. suggests that habitual fainting may be two to eight times *less* common in the elderly compared to young individuals [18].

Overlap between neurological and psychiatric terminology for fear-induced fainting was demonstrated by Accurso et al. [1]. They compared 9 females and 2 males who experienced habitual syncope or presyncope (only in response to blood or injury) with 11 sex-matched controls [1]. They found no difference at rest. In contrast, during head-up tilt, 82 % of blood phobic subjects experienced presyncope or syncope. Only 9 % of the controls experienced presyncope during tilt ($P = 0.001$) [1]. They concluded that blood-injury syncope subjects have an underlying constitutional predisposition for neurally mediated fainting and that this heritable predisposition for habitual fainting later leads to secondary phobic fear of bloodletting because of the repeated traumatic fainting episodes [1]. We speculate that in that sense, blood-injection-injury phobia is akin to post-traumatic stress disorder (PTSD) [5].

Newton et al. called attention to the high heritability of habitual fainting [18]. Among their 603 participants, 19 % reported positive family history of blackouts or faints. Newton et al. also found a high prevalence of vasovagal fainting among first-degree relatives of those with a definitive diagnosis of vasovagal syncope. Unlike earlier studies [14]. They required symptom reproduction during a positive head-up tilt. Eleven first-degree relatives were given head-up tilt testing with glyceroltrinitrate provocation and all had symptoms in response to head-up tilt. A recent twin study also demonstrated the very high heritability of fear-induced fainting [20].

Mid-paleolithic threats, fear, and fainting

A widely-held hypothesis regarding bloodletting-related fainting assumes that fainting increases the probability of survival through initiation of a drop in blood pressure, thus minimizing blood loss [19]. This, however, cannot explain fainting in response to injection, sharp pain, or fright [19]. Furthermore, hemodynamically based fainting only occurs after a 30 % drop in blood volume [2]. Vasoconstriction and tachycardia (rather than vasodilatation and bradycardia) are the adaptive initial responses to blood loss [2].

To our knowledge, the Paleolithic-Threat hypothesis is the first to tackle several unusual aspects of fear-induced fainting [5]. It posits that fear-induced fainting evolved in response to human warfare during the Mid-Paleolithic and that fear-induced fainting is mediated by human-specific neural circuits arising via what Darwin termed "sexual selection" ("mate selection" or "mate choice"). Recent reviews suggest that several human-specific limbic circuits were prepotentiated or hard-wired as stable (balanced) polymorphisms during the Mid-Paleolithic by this particular subtype of evolutionary selection [8, 9, 15].

The myth of the "noble peaceful savage"

The widely held popular notions that human warfare first emerged in historical times and that we evolved from peaceful savages have been proven false [13]. Extensive inter-clan violence took place in the Mid-Paleolithic [13]. Skeletal remains reveal that a common cause of death in the Mid-Paleolithic was a penetrating wound from a sharp object. Bio-anthropological studies, and recent mtDNA and chromosome Y studies of female and male lineages, respectively, also find a marked sex difference in the cause of death in the Mid-Paleolithic. It has been estimated that during inter-clan warfare, victors killed 15 %–50 % of post-pubertal males [13], and took females and most pre-pubertal individuals captive. Therefore, fear-induced fainting was probably highly maladaptive for Mid-Paleolithic post-pubertal males, resulting in death or lower mate availability. In contrast, fear-induced fainting may have been adaptive for females and pre-pubertal individuals, since it increased the likelihood of survival [5].

Testable predictions and possible implications

Several testable predictions follow from the Paleolithic-Threat hypothesis. These may have implications for clinical research and may also provide a plausible genetic and trancriptomic model regarding the age and sex patterns of fear-induced fainting.

- Glucocorticoid and mineralocorticoid receptors are extensively studied by both autonomic nervous system and fear-circuitry researchers. One contribution of the Paleolithic-Threat hypothesis is that it may encourage expansion of this research into the role of androgens in the above two areas.
- Fear-induced fainting has an age and sex pattern rarely found in other syncopal conditions. Neurocardiological researchers with access to large samples of patients may be able to examine sex differences while controlling for age. The most recent epidemiological study of 1,920 subjects with blood-injection-injury fears found an overall female-to-male ratio of 2.4 to 1 [3]. This ratio may be higher if a sample is limited to the age range when sex differences in androgen levels are highest.
- In light of the hypothesized role of androgens, the following clinically testable predictions can be made: Vasovagal fainting may often spontaneously remit shortly after menopause. We are unaware of any published data addressing this hypothesis. In addition, hypo-androgenic subjects may manifest significantly more vasovagal fainting than sex-matched controls, and hyper-androgenic subjects may manifest significantly less vasovagal fainting than sex-matched controls. Finally, a change in the susceptibility to vasovagal fainting may be demonstrable in clinical studies that involve treatment with anti-androgenic agents, or with androgenic agents such as testosterone or dehydroxyepiandrosterone sulfate.
- The median age of onset of fear-induced fainting is 5.5 years. Research may be able to demonstrate a female-to-male ratio closer to one in pre-pubertal individuals [3].
- Some neuroevolutionary hypotheses can be empirically tested by primatologists [17]. We predict that non-human primates, regardless of age and sex, would not be shown to have bloodletting-induced fainting. Surprisingly, there are no published studies that address this question.

It would be premature to make any clinical recommendations based on this hypothesis. However, the Paleolithic-Threat hypothesis is consistent with the technique developed by Mathias (personal communication) of presenting a syringe with a large needle to habitually fainting individuals regardless of needle phobia history. Studies of this interesting cost-effective technique are warranted.

Finally, the understanding of the human acute alarm-response sequence has advanced considerably since it was first described in 1929 (reviewed by Bracha [4–6]). A review of all the psychiatric aspects of Paleolithic-Threat hypothesis is outside the scope of this article. However, the Paleolithic-Threat hypothesis may have implications for PTSD research, and for research in the aftermath of man-made disasters, such as terrorism against civilians, a traumatic situation in which our hypothesis predicts epidemics of fear-induced fainting.

Conclusion

We posit that fear-induced (threat-induced) fainting is traceable to allelic stable polymorphisms selected into some human genomes because of the survival advantage it conferred to Mid-Paleolithic non-combatants in situations involving inescapable threat. One important contribution of the Paleolithic-Threat hypothesis may be that it predicts a testable link to various normative and pathological hypo-androgenic states.

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