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SCIENCE DIRECT
Progress in Neuro-Psychopharmacology & Biological Psychiatry 30 (2006) 827–853
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Review article

Human brain evolution and the "Neuroevolutionary Time-depth Principle:" Implications for the Reclassification of fear-circuitry-related traits in DSM-V and for studying resilience to warzone-related posttraumatic stress disorder

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Accepted 10 January 2006
Available online 23 March 2006

Abstract

The DSM-III, DSM-IV, DSM-IV-TR and ICD-10 have judiciously minimized discussion of etiologies to distance clinical psychiatry from Freudian psychoanalysis. With this goal mostly achieved, discussion of etiological factors should be reintroduced into the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V). A research agenda for the DSM-V advocated the "development of a pathophysiologically based classification system". The author critically reviews the neuroevolutionary literature on stress-induced and fear circuitry disorders and related amygdala-driven, species-*atypical* fear behaviors of clinical severity in adult humans. Over 30 empirically testable/falsifiable predictions are presented. It is noted that in DSM-IV-TR and ICD-10, the classification of stress and fear circuitry disorders is neither mode-of-acquisition-based nor brain-evolution-based. For example, snake phobia (innate) and dog phobia (overconsolidational) are clustered together. Similarly, research on blood-injection-injury-type-specific phobia clusters two fears different in their innateness: 1) an arguably ontogenetic memory-trace-overconsolidation-based fear (hospital phobia) and 2) a hardwired (innate) fear of the sight of one's blood or a sharp object penetrating one's skin. Genetic architecture-charting of fear-circuitry-related traits has been challenging. Various, non-phenotype-based architectures can serve as targets for research. In this article, the author will propose one such alternative genetic architecture. This article was inspired by the following: A) Nesse's "Smoke-Detector Principle", B) the increasing suspicion that the "smooth" rather than "lumpy" distribution of complex psychiatric phenotypes (including fear-circuitry disorders) may in some cases be accounted for by oligogenic (and not necessarily polygenic) transmission, and C) insights from the initial sequence of the chimpanzee genome and comparison with the human genome by the Chimpanzee Sequencing and Analysis Consortium published in late 2005. Neuroevolutionary insights relevant to fear circuitry symptoms that primarily emerge overconsolidationally (especially Combat related Posttraumatic Stress Disorder) are presented. Also introduced is a human-evolution-based principle for clustering innate fear traits. The "Neuroevolutionary Time-depth Principle" of innate fears proposed in this article may be useful in the development of a neuroevolution-based taxonomic re-clustering of stress-triggered and fear-circuitry disorders in DSM-V. Four broad clusters of evolved fear circuits are proposed based on their time-depths: 1) Mesozoic (mammalian-wide) circuits hardwired by wild-type alleles driven to fixation by Mesozoic selective sweeps; 2) Cenozoic (simian-wide) circuits relevant to many specific phobias; 3) mid Paleolithic and upper Paleolithic (*Homo sapiens*-specific) circuits (arguably resulting mostly from mate-choice-driven stabilizing selection); 4)

Abbreviations: WR-PTSD, warzone-related posttraumatic stress disorder; FOXP2, forkhead box p2; TCG, transcription controller-gene; Indels, genomic insertion/deletion events; HPIL, hereditary persistence of intestinal lactase; ASPM, abnormal-spindle-like, microcephaly-associated; MCPH, microcephaly primary autosomal recessive; CSAC, the Chimpanzee Sequencing and Analysis Consortium; DHEA-S, dehydroxyepiandrosterone sulfate; BP, base pairs; SINEs, short interspersed repeats; SNPs, single nucleotide polymorphisms; MRCA, most recent common ancestor; FIMS, fear-induced malignant syncope; LC, locus coeruleus; BLNA, basolateral-nucleus-of-the-amygdala; EEA, environment of evolutionary adaptedness; Neuroevolutionary-TDP, Neuroevolutionary Time-depth Principle; ECA, epidemiological catchment area; NCS, National Comorbidity Survey; ICD, International Classification of Disease; NE, norepinephrine; DSM-III, DSM-IV, DSM-IV-TR, DSM-V, Diagnostic and Statistical Manual of Mental Disorders III, IV, IV-text revision, and V; OCD, obsessive-compulsive disorder; PTDA, Posttraumatic Dental-care Anxiety; ASD, acute stress disorder; Mya, million years ago; Kya, thousand years ago; YA, years ago; WWII, world war two; VA, Veterans Affairs; C&P exam, compensation and pension examination.

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0278-5846/$ - see front matter. Published by Elsevier Inc.
doi:10.1016/j.pnpbp.2006.01.008

Neolithic circuits (arguably mostly related to stabilizing selection driven by gene–culture co-evolution). More importantly, the author presents evolutionary perspectives on warzone-related PTSD, Combat-Stress Reaction, Combat-related Stress, Operational-Stress, and other deployment-stress-induced symptoms. The Neuroevolutionary Time-depth Principle presented in this article may help explain the dissimilar stress-resilience levels following different types of acute threat to survival of oneself or one's progency (aka DSM-III and DSM-V PTSD Criterion-A events). PTSD rates following exposure to lethal inter-group violence (combat, warzone exposure or intentionally caused disasters such as terrorism) are usually 5–10 times higher than rates following large-scale natural disasters such as forest fires, floods, hurricanes, volcanic eruptions, and earthquakes. The author predicts that both intentionally-caused large-scale bioevent-disasters, as well as natural bioevents such as SARS and avian flu pandemics will be an exception and are likely to be followed by PTSD rates approaching those that follow warzone exposure. During bioevents, Amygdala-driven and locus-coeruleus-driven epidemic pseudosomatic symptoms may be an order of magnitude more common than infection-caused cytokine-driven symptoms. Implications for the red cross and FEMA are discussed. It is also argued that hospital phobia as well as dog phobia, bird phobia and bat phobia require re-taxonomization in DSM-V in a new "overconsolidational disorders" category anchored around PTSD. The overconsolidational spectrum category may be conceptualized as straddling the fear circuitry spectrum disorders and the affective spectrum disorders categories, and may be a category for which Pitman's secondary prevention propranolol regimen may be specifically indicated as a "morning after pill" intervention. Predictions are presented regarding obsessive-compulsive disorder (OCD) (e.g., female-pattern hoarding vs. male-pattern hoarding) and "culture-bound" acute anxiety symptoms (taijin-kyofusho, koro, shuk yang, shook yong, suo yang, rok-joo, jinjinia-bemar, karoshi, gwarosa, Voodoo death). Also discussed are insights relevant to pseudoneurological symptoms and to the forthcoming Dissociative-Conversive disorders category in DSM-V, including what the author terms *fright-triggered acute pseudo-localized symptoms* (i.e., pseudoparalysis, pseudocerebellar imbalance, psychogenic blindness, pseudoseizures, and epidemic sociogenic illness). Speculations based on studies of the human abnormal-spindle-like, microcephaly-associated (*ASPM*) gene, the microcephaly primary autosomal recessive (*MCPH*) gene, and the forkhead box p2 (*FOXP2*) gene are made and incorporated into what is termed "The pre-*FOXP2* Hypothesis of Blood-Injection-Injury Phobia." Finally, the author argues for a non-reductionistic fusion of "distal (evolutionary) neurobiology" with clinical "proximal neurobiology," utilizing neurological heuristics. It is noted that the value of re-clustering fear traits based on behavioral ethology, human-phylogenomics-derived endophenotypes and on ontogenomics (gene–environment interactions) can be confirmed or disconfirmed using epidemiological or twin studies and psychiatric genomics.
Published by Elsevier Inc.

Keywords: Allele-variant polymorphisms; Anxiety disorders; Combat-related PTSD; DSM-V; Large-scale disaster; Phobias; Stress and fear circuitry disorders; War

Contents

1. Introduction: the three goals of this articles

Pitman and Delahanty (2005) have recently emphasized the importance of conceptually driven approaches to stress and fear circuitry disorders research. This conceptually driven article has three main purposes. The first and most important purpose is to present testable predictions which can be falsified in existing databases or in future studies. The second purpose of this article is to attempt to tackle some remaining language barriers between anxiety disorder researchers and evolutionary neurobiologists. The third purpose of this article is to look at the field's conventional wisdom from a new angle, and to propose useful concepts based on research from seemingly distant scientific disciplines. The article's title was inspired by Nesse and Williams' "Smoke-Detector Principle" of anxiety, which introduced into psychiatry a highly useful concept based on principles of financial cost–benefit analysis in economics and principles of signal detection analysis in psychophysics.

1.1. Goal 1: twenty predictions based on hypothesized neuroevolutionary factors

The author reviews the relevant literature, and presents over 30 empirically testable and falsifiable predictions based on hypothesized neuroevolutionary factors in the etiology of fear-circuitry-related traits. Neuroevolutionary psychiatry, like its

Table 1
Relevant terms from the new paleo-anthropological consensus terminology

New consensus terminology (Dawkins, 2004)	Description
Hominids	The lineage that includes genus *Homo* and genus *Pan* but not other apes
Hominins	The human lineage following the genus *Homo*/ genus *Pan* divergence (split) from their most recent common ancestor (MRCA) 5 million years ago (Mya)
Australopithecines [Australopiths]	*Australopithecus afarensis* (and numerous other terms)
Homo ergaster [Ergasts]	African *Homo erectus* (pre-2004 terminology)

sister specialty evolutionary psychology, is not a belief system but a research program, and each behavioral trait must be tested before neuroevolutionary etiologies are accepted (Cosmides and Tooby, 1999, 1992). The null hypothesis is always that a particular anxiety-related trait is not an evolved limbic circuit, but rather an evolutionary design compromise, an evolutionary by-product, a "spandrel" or a stochastic manifestation of genetic drift. Regarding the testability of clinical evolutionary hypotheses, also see Nesse (1999). For clinical reviews, see Nesse (2001a), McGuire and Troisi (2000) and McGuire et al. (1992). It should be noted that, unlike neuroevolutionary psychiatry, evolutionary psychology defines itself as a non-clinical field and claims limited use for clinical care or for psychiatric genetics (Tooby and Cosmides, 2005; Cosmides and Tooby, 1999, 1992). By definition, evolutionary psychology focuses on universal human traits which are species-typical in humans and thus have low heritability (Tooby and Cosmides, 2005; Cosmides and Tooby, 1999, 1992). In contrast, neuroevolutionary psychiatry, the focus of this article, attempts to offer clinically useful predictions relevant to the research agenda for the DSM-V. Neuroevolutionary psychiatry may also be useful to psychiatric genetics and for research on the human-clade phylogenomics–ontogenomics (gene–environment) interface. The *overarching hypothesis* relevant to clinical anxiety disorders presented herein is that some vanishingly rare brain-expressed allele variants that previously had little survival value (or were deleterious) increased by two or three orders of magnitude during the mid–upper Paleolithic and Neolithic EEA due to new recurring selective pressures that had little effect on earlier hominins or on non-human simians. Several authorities have previously made related observations with regard to non-psychiatric physiological conditions (OMIM, 2004; Hollox et al., 2001; Harvey et al., 1998; Holden and Mace, 1997; Cavalli-Sforza et al., 1994).

1.2. Goal 2: tackling a few of the terminological barriers

The second purpose of this article is to tackle a few remaining language barriers between anxiety disorder researchers and evolutionary neurobiologists. One terminological barrier may be the lack of clarity among physicians of the technical definition of words such as "maladapted," "adapted," and "adaptation" in the evolutionary biology literature. These terms originated with Darwin, and are used in the evolution literature to refer to "evolved traits." In contrast, most clinicians use the colloquial ontological meaning of these terms (which are approximately synonymous with "maladjusted," "well-adjusted," and "adjustment," respectively). To minimize confusion, the author uses the terms "evolved fear circuits" in lieu of "fear adaptations," and "non-fitness-enhancing" in lieu of "maladaptive." Another source of confusion is that the paleoanthropological terminology has been in flux until very recently. The terminology used in this article is the new consensus terminology (Dawkins, 2004; Wood and Richmond, 2000) (Table 1). Some speculations about how to incorporate the neuroevolutionary "why" and "when" questions into fear circuitry disorders research to produce a comprehensive (who, what, when, where, why, how) investigational approach are presented in Table 2. The four time-depths cited in this article (12,000 years ago [YA], 70,000 YA, 20 million years ago [Mya] and 140 Mya) are based on research recently reviewed by Dawkins (2004).

1.3. Goal 3: reexamining "ancestral fears" as relevant to fear circuitry disorders

The author's third purpose is to reexamine terms such as "ancestral environment" and "ancestral fears" in light of: a) new research on the *Pan troglodytes* genome emerging from the Chimpanzee Sequencing and Analysis Consortium (CSAC) data and b) research on hominin evolution recently reviewed by Richard G. Klein (see recent review by Klein and Edgar, 2002). Terms such as "ancestral environment" erroneously suggest that the hominin EEA since the *Homo*/*Pan* divergence was a consistent environment. Terms such as "ancestral fears" fail to make the arguably important differentiation between

Table 2
Incorporating the neuroevolutionary, "why" and "when" questions into the spectrum of research approaches investigating the etiology of evolved fear-circuitry-related traits

Research approach	Key question, e.g., who, what, when, where, why, how and/or key investigational methodology
Adoption study	*What?* Genetic transmission
Twin study	*How?* Heritability
Genetic linkage	*Where?/Who?* Co-segregation of marker and disease
Genetic association	*How?/Who?/Where?* Allele frequencies
Human proteomics and transcriptomics	*How?/Who?/Where?* Epigenetics, gene-expression profiling, etc.
Human genomics	*How?/Who?/Where?* Sequencing, physical mapping, etc.
Human phylogenomics and neuroevolutionary psychiatry	*Why?* *Why* did these allele frequencies, gene-dosages and gene-regulatory regions evolve? *Why?* *Why* were these particular ones highly conserved? *When?* *When* did the these allele frequencies, gene-dosages and gene-regulatory regions evolve? Key methodology: conceptually-driven hominin phylogenomics

limbic circuits of different time-depths (e.g., limbic circuits that extant humans share with all simians, versus limbic circuits dating back only to Neolithic and upper Paleolithic *H. sapiens*). This article, therefore, divides evolved fear circuitry traits which outlived usefulness (and are thus clinically relevant), by their neuroevolutionary time-depth into four broad subgroups (Table 3):

1) Mesozoic Era mammalian-wide evolved fear circuits
2) Cenozoic Era simian-wide evolved fear circuits
3) Mid and upper Paleolithic *H. sapiens*-wide evolved fear circuits
4) Neolithic culture-bound-genome-specific (gene–culture co-evolution-based) fear circuits.

The "Neuroevolutionary Time-depth Principle" presented in this paper is inspired in part by Richard G. Klein's theory of the emergence of culture (Klein and Edgar, 2002). Klein argued that hominin neuroevolution since the *Homo*/*Pan* divergence was so strongly punctuated by numerous macro-mutations (single brain expressed mutations of large effect) that the division into epochs is less arbitrary than previously believed.

2. Emerging empirical evidence

2.1. Experimental studies comparing evolutionarily relevant and evolutionarily neutral stimuli

Experimental research on neuroevolutionary (distal/ultimate) etiologies of fear-circuitry-related traits is still limited. However, a good number of comprehensive reviews have been published (Poulton and Menzies, 2002; Ohman and Mineka, 2001; Nesse, 1999; Wakefield, 1992; Cook and Mineka, 1990; Marks and Tobena, 1990; Marks, 1987). Fear of high elevations was the first mammalian-wide (Mesozoic-era) hardwired fear-circuit empirically documented by Gibson and Walk (1960). Gibson and Walk's "visual cliff experiment" demonstrated that both human toddlers and day-old goats will not walk on a transparent solid surface that gives the impression of walking off a cliff. Clinical studies have similarly supported the innateness of the fear of heights (Poulton et al., 1998; Menzies and Clarke, 1993). Mammalian-wide hardwired fears, such as fear of heights, are naturally of less interest to anxiety disorders researchers. These are generally considered to be "normal fears" and probably have been wired by alleles driven to fixation. Firm-wired Cenozoic era fear circuits (simian-wide prepotentiated fear traits) are

Table 3
Neuroevolutionary time-depth-driven re-clustering of fear-circuitry-related traits proposed for DSM-V

Human-species-atypical (thus often clinically-relevant) symptom	Posited neuroevolutionary time-depth of circuit	Approximate heritability predicted based on evolutionary reasoning alone
Extreme fear of adult non-kin males in toddlers Extreme fear of high elevations in adults	MESOZOIC Mammalian-wide 140,000,000 years	0-10%
Fear of snakes Fear of reptiles/crocodiles/alligators Fear of confined spaces Fear of darkness Fear of water immersion CO_2-induced panic attack (fear of suffocation during forest fire?) Lactate-induced panic attack (fear of muscle exhaustion while under predation?) Acute-fear-induced jaw-clenching and chronic stress-induced incisor-grinding	CENOZOIC Simian-wide 20,000,000 years	20–40%
Compulsive lock checking Compulsive stove checking Compulsive washing and obsessive fear of contamination Compulsive hoarding (especially of tools, weapons and leather goods) Extreme fear of insects or mice Fear of scrutiny by non-kin conspecifics (Generalized Social Phobia)	UPPER PALEOLITHIC Neurally modern *H. sapiens* 70,000 years	40%
UNLOCALIZED (PSEUDO-SOMATIC) SYMPTOMS IN THE CONVERSIVE-DISSOCIATIVE-SPECTRUM PROPOSED FOR DSM-V: e.g., Pseudo-cytokine-driven (pseudo-infectious) fear symptoms Epidemic pseudo-cytokine-driven (pseudo-infectious) fear symptoms Primary dissociative disorder? *PSEUDO-LOCALIZED (PSEUDONEUROLOGICAL "CONVERSIVE") SYMPTOMS:* Psychogenic non-epileptic attacks (pseudoseizures) Epidemic sociogenic illness "epidemic hysteria" Psychogenic pseudoparalysis (e.g., limping) Psychogenic imbalance (Pseudocerebellar symptoms) Psychogenic blindness	NEOLITHIC 12,000 years	40%

somewhat more relevant to anxiety disorders research than the mammalian-wide (rational fear) circuits. Simian-wide prepotentiated fears were first empirically documented in two experiments by Cook and Mineka (1989). In the first experiment, they examined whether observer rhesus monkeys would acquire fear responses to evolutionarily relevant stimuli (toy snakes) as compared to evolutionarily neutral stimuli (artificial flowers) after a single viewing of a videotape showing model conspecifics behaving fearfully. Laboratory-reared rhesus monkeys were used to control for prior ontogenetic experiences. Novel stimuli were used for evolutionarily relevant and evolutionarily neutral conditioned stimuli. In the first study, "snake observer monkeys" acquired fear of toy snakes simply through observational conditioning. By contrast, "flower observer monkeys" watching exactly the same fear performance toward brightly colored artificial flowers did not acquire a fear of flowers. In the second experiment, observational conditioning resulted in rhesus monkeys acquiring a fear of a toy crocodile but not of a toy rabbit. In both studies, this differential conditioning of fear to evolutionarily relevant objects (toy snake and toy crocodile) was maintained beyond a single laboratory session (Cook and Mineka, 1989). The authors concluded that differences in the associability of evolutionarily relevant and evolutionarily neutral stimuli derive primarily from phylogenetic rather than ontogenetic factors. Cook and Mineka conclude that simians, both human and non-human, may have a phylogenetically prepotentiated predisposition to acquire instantaneously fears of certain objects or situations that may once have posed a life threat to early simian ancestors. They have cogently argued that this predisposition is derived from the selective advantage that those simian ancestors who had rapidly acquired fears of such objects or situations would have had over conspecifics who had not. The scarcity of simians for behavioral research is the main impediment to further enlarging the science base in this field. Buss et al. (Buss, 1999; Buss et al., 1998) list 30 examples of neuroevolutionary-relevant findings that have been empirically derived and widely replicated. Some of these include superior color vision and superior spatial location memory in females, and superior ability to detect, track and predict animate motion in males. Most of these studies were done in non-clinical settings using college students and few involve psychopathology. This is partly because such studies usually require large samples and reliable self-report.

2.2. Epidemiological evidence: toddlers' fear of adult non-kin male conspecifics

Most psychosocial studies of Posttraumatic Stress Disorder (PTSD) following intra-household child abuse fail to use the standard anthropological rule of differentiating between step-child abuse and offspring abuse. In a 1988 paper in Science which used this differentiation (Daly and Wilson, 1988) the authors provided evidence that a toddler's fear of "mother's new boyfriend" is most likely an evolved fitness-enhancing fear circuit. Evolutionary psychologists Daly and Wilson reviewed studies of "family homicides," since they do not depend on self-report. They found that "19% of Detroit victims in 1972 were related to their killers by marriage compared to only 6% by blood, and 10% of Miami victims in 1980 were marital relatives of their killers compared to 1.8% blood relatives" (Daly and Wilson, 1988). In the Detroit study they reported, "Coresidents related to the killer by blood, whether spouses or not, were more than 11 times more likely to be slain than coresiding genetic relatives" (Daly and Wilson, 1988). It is unclear how frequently public policy implications of this research are implemented. To this author, Daly and Wilson's landmark studies suggest that "intrafamily child abuse" is actually a misnomer and that the term "step-child abuse" is a better description of the data. Daly and Wilson also note that, "presently available data do not reveal whether stepmother or stepfather households entail greater risks" (Daly and Wilson, 1988), and that there is insufficient exploration of emotional abuse and neglect of stepchildren by abusive stepmothers. Abusive stepmothers are anecdotally reported in most ethnocultural groups studied. Unfortunately, transcultural and ethnic studies rarely provide quantitative data. Among the foraging Ache of Paraguay, "of 67 children raised by a mother and stepfather after the natural father's death: 43% had died, of various causes, before their 15th birthdays, as compared to just 19% of those raised by two surviving parents" (Daly and Wilson, 1988). It is unfortunate that many clinical studies do not use the standard anthropological rule of differentiating between step-child abuse and offspring abuse, because such differentiation may clarify some contradictory findings regarding early abuse and subsequent PTSD. Throughout the mammalian class, intense fear of non-kin adult male conspecifics is widely documented in unweaned mammals. Among chimpanzees, gorillas and orangutans, a non-kin adult male conspecific is a common perpetrator of infanticide (and of "toddlericide") when encountering an unrelated female of reproductive age caring for an unweaned infant or toddler. (The observation that some toddlers also fear adult males who are blood relatives may be another example of Nesse's Smoke-Detector Principle, described below.) In other words, a survival enhancing Type-1 error (Brugger, personal communication).

2.3. Twin studies of fear-circuitry-related traits

A series of landmark twin studies by Kendler and colleagues (e.g., 2001) provide empirical support for the evolutionary etiology of most phobias. These studies have been lucidly reviewed elsewhere (Hettema et al., 2003, 2001; Kendler et al., 2001, 1992; Neale et al., 1994). Irrational fears examined by Kendler et al. (2002) include, among others, fear of open spaces, crowds, new people, public speaking, public bathrooms, eating in public, spiders, bugs, mice, snakes, bats, other animals, tunnels, other closed spaces, bridges, airplanes, other high places, blood, needles/injection, dentist/hospitals, and diseases (Kendler et al., 2002). In their seminal paper "The etiology of phobias," which reported results from over 7500 twins, Kendler et al. (2002) conclude that overall, their results "…are more consistent with nonassociative models of phobia acquisition than with traditional etiologic theories involving conditioning or

social transmission." Kendler et al. (2002) also note that "…a growing body of data from both retrospective and prospective studies that suggest that most phobias are acquired nonassociatively (i.e., without the involvement of learning). This theory suggests that the liability to phobias is innate, having arisen from evolutionary selection…" (Kendler et al., 2002). Neuroevolutionary psychiatry assumes that both common allele variants and subtype-specific allele variants contribute to irrational fears and phobias. Population genetics and twin studies of irrational fears and phobias conclusively demonstrate that these are polygenic or, at best, oligogenic. The study of Kendler et al. (2001) in which they conducted in-person interviews with both members of 1198 male–male twin pairs (707 monozygotic and 491 dizygotic) is the most relevant in the context of this article. The only two phobias in which Kendler et al. (2001) found that family environment may have an impact on risk are agoraphobia and social phobia.

3. A brief overview of ongoing hominin phylogenomic studies: the Chimpanzee Sequencing and Analysis Consortium

Human phylogenomics is arguably the basic science of evolutionary neuropsychiatry, and became a reality in late 2005 with the completion of the first step of the *P. troglodytes* (common chimpanzee) genome study by the Chimpanzee Sequencing and Analysis Consortium (CSAC, 2005). The CSAC study included the whole-genome shotgun sequencing of the chimpanzee genome, and more importantly, the genome-wide comparison of recent chimpanzee and human segmental duplications. No CSAC data specifically relevant to stress resilience and to fear-circuitry-related traits are published as of late 2005, but such data are expected to emerge at a rapid pace. It is arguably axiomatic that the vast majority of genomic differences between the two extant hominids (*Pan* and *Homo*) are in brain-expressed regions of the genome. Neuroevolutionary psychiatry may thus be one of the medical subspecialties that will benefit the most from the sequencing of the *P. troglodytes* genome by the CSAC (2005). To date, numerous important general insights into human genomic neuroevolution emerged from the CSAC (2005). For example, as expected, little evidence was found to suggest that the addition of novel gene loci was a major mechanism in human brain evolution. Also, as expected, Alu elements (short interspersed repeats [SINEs]) have been threefold more active in humans since the *Homo*/*Pan* divergence. Also, some indirect support was given to the exon-deletion "less is more hypothesis" which posits that some loss-of-function mutations or deletions may have been responsible for the tripling of brain size which marked the transition from Australopiths to *H. ergaster* circa 200 Mya (conceivably by a failure of a suppressor gene which, in the Australopiths, stopped the division of cortical progenitor cells after probably 100 cell divisions and allowed a several fold increase in cortical progenitor cell divisions). Finally, paleogenomics gene-expression studies from the CSAC provide insights into pitfalls which gene-expression studies of postmortem brain tissue in PTSD may encounter (Khaitovich et al., 2005).

3.1. Evolution of non-protein-coding gene-regulatory regions

One finding from the CSAC (2005) with potential future treatment implications is that non-protein-coding promoter regions responsible for complex modulation of existing alleles (e.g., at the transcriptome level) undergo changes as a result of evolutionary pressures and are probably more important than protein evolution (by amino acid substitutions) (Li and Saunders, 2005). CSAC data confirm that changes in messenger RNA and protein expression levels play a much greater role in hominin evolution than the non-synonymous DNA changes that alter amino acid sequences (Cheng et al., 2005; Hill and Walsh, 2005). Single nucleotide polymorphisms (SNPs) in these gene-regulatory regions can thus be explored within a neuroevolutionary framework. Commenting on the CSAC findings regarding the evolution of the non-protein-coding promoter regions, Li and Saunders (2005) state that:

> The hypothesis invoking evolution in gene-regulating regions is currently the hardest to test. Yet it may be the most promising given what we know of human biology relative to that of apes (Li and Saunders, 2005).

3.2. Elevated gene dosage of harm-avoidance genes common to all irrational fear and phobia subtypes (and all anxiety disorders?): too much of a good thing

DSM-V is likely to conceptualize fear circuitry disorders as dimensional/continuous rather than categorical. In this context, it is arguable that the genome-wide comparison of recent chimpanzee and human segmental duplications by the CSAC is especially relevant (CSAC, 2005). It is axiomatic that the underlying genetic transmission of stress-triggered and fear circuitry disorders is either polygenic or, as it increasingly seems, oligogenic. The CSAC data suggest that gene dosage is an important factor in conceptualizing continuous behavioral traits. Examination of the 33% of human-duplicated segments which are human-specific found that, compared to *P. troglodytes*, it is humans who typically have the increased gene dosage. Five million indels (insertion/deletion events) and numerous large segmental duplication events (4–5 megabases per million years) have been found to have occurred in genus *Homo* since the *Homo*/*Pan* divergence 5 Mya (CSAC, 2005). This is consistent with the Kendler et al. (2001) data on irrational fears and phobias concluding that genetic risk factors that play a role in the etiology of phobias and their associated irrational fears are partially *common across all subtypes* and partially subtype-specific.

3.3. "Phobia subtype-specific" DNA changes. Possible insights from research on abnormal-spindle-like, microcephaly-associated (ASPM), microcephaly primary autosomal recessive (MCPH), and forkhead box P2 (FOXP2) loci

More important in the context of this article is Kendler et al.'s (2001) conclusion that any allele variants involved in irrational fears and phobias are also "partially subtype-specific" (p. 257).

Additionally, there is increasing suspicion that the "smooth" rather than "lumpy" distribution of a psychiatric phenotype in the population may in some cases be accounted for by oligogenic (and not necessarily polygenic) transmission. Until very recently, Richard G. Klein's hypothesis (Klein and Edgar, 2002) that hominin neuroevolution since the *Homo*/*Pan* divergence was strongly punctuated by mutations of relatively large effect would have been objected to by some authors who have maintained that the division of a nearly continuous (albeit punctuated) process such as human evolution into epochs is completely arbitrary. Thus, it is important in the context of the time-depth principle that the Chimpanzee Sequencing and Analysis Consortium data (CSAC, 2005) provide strong support for Richard Klein's conclusion that post-*Homo*/*Pan* divergence neuroevolution was strongly punctuated by brain-expressed mutations of moderate or large effect in the human lineage, thus providing indirect support for the deconstruction of the "ancestral fears environment" into four somewhat distinct subgroups, as conceptualized here by the Neuroevolutionary Time-depth Principle. For example (consistent with Klein's hypothesis), the CSAC study has found that 73% of the affected base pairs since *Homo*/*Pan* divergence are in indels larger than 80 bp (insertable transposable elements, microsatellites, and deletions). Commenting on the CSAC data, Li and Saunders (2005) state that

> Given the short time since the human–chimpanzee split, it is likely that a few mutations of large effect are responsible for part of the current physical–phenotypic-differences that separate humans from chimpanzees and the great apes.

Psychiatric molecular geneticists should draw encouragement from the fact that the same conclusion is at least as likely to be drawn for phenotypic differences which are brain-expressed (i.e., cognitive and behavioral). For example, the *ASPM* and *MCPH* genes have been strongly implicated in primary microcephaly in extant humans. These are increasingly considered to be a reversal of a string of advantageous loss-of-function brain-expressed mutations of large effect which occurred circa 2 Mya and via a selective sweep, replaced the Pliocene Australopiths with the early Paleolithic Ergasts (Kouprina et al., 2004; Evans et al., 2005; Mekel-Bobrov et al., 2005). Unsurprisingly, Australopith brain size (around 400 cm^3) is identical to that of extant microcephalic humans. Of special interest in the context of this article are the forkhead box p2 (*FOXP2*) gene mutations (Nokelainen and Flint, 2002), likely to belong among the major advantageous brain-expressed mutations of large effect responsible for the sudden appearance of the (speech enabled) neurally modern *H. sapiens* circa 70 Kya and thus ushered in the upper Paleolithic. Also of great importance in the context of this article is that the technologies developed by *MCPH*, *ASPM*, *FOXP2* and other CSAC studies (2005) are also suitable for identifying foot-prints (signatures) of positive selection in brain-expressed genome regions that occurred in the upper Paleolithic and even in the Neolithic (e.g., those leading, via recent stabilizing selections, to fear-circuitry-related balanced polymorphisms). This has been demonstrated by the studies of Kouprina et al. (2004), Evans et al. (2005), and Mekel-Bobrov et al. (2005). Due to the ongoing thawing of the Siberian, North Russian and Scandinavian permafrost, large quantities of perfectly preserved *H. sapiens* DNA (and of *H. sapiens* RNA and *H. sapiens* enzymes) from possibly hundreds of individuals are likely to be found. Molecular archeogenomic data relevant to fear circuitry disorders in general are likely to emerge and may also confirm or disconfirm (with near forensic certainty) the neuroevolutionary time-depth assignments proposed here for various evolved fear circuitry traits. For example, the techniques developed in the Evans et al. (2005) *MCPH* study demonstrating that one variant emerged circa 37 Kya can be applied to studying genomic mechanisms involved in the group of fear circuitry traits which are posited here to be of upper Paleolithic time-depth (such as compulsive hoarding and social phobia), and to genomic mechanisms involved in PTSD resilience.

4. Fear-circuitry-related traits in DSM-V and the "Neuroevolutionary Time-depth Principle"

Charting the genetic architecture of fear-circuitry-related traits such as specific phobias has been an important but challenging enterprise. The Specific Phobias section in the earlier versions of DSM (APA, 1980, 1994, 2000) is neither mode-of-acquisition-based nor brain-evolution-based (Table 4). For example, DSM-IV-TR (APA, 2000) blood-injection-injury-type-specific phobia clusters two fears arguably different in their mode of acquisition: 1) a PTSD-like ontogenetic fear overconsolidation (avoidance of hospitals) and 2) an innate ~70,000 y/o fear circuit (the sight of blood or an approaching sharp object). "Animal Type Specific Phobia" clusters three irrational fears different in their mode of acquisition and/or in their time-depth: 1) an overconsolidational fear of dogs (*unlikely* to be innate considering the 15,000 year long symbiotic co-

Table 4
Inconsistencies within the phenotype-based DSM-IV-TR classification of irrational fears (in regard to the mode-of-acquisition and neuroevolutionary time-depth)

DSM-IV-TR specific phobia traditional classification:	Primary mode-of-acquisition and the posited neuroevolutionary time-depth if mostly innate
"BLOOD/INJECTION INJURY"	FEAR OF HOSPITALS: A PTSD-like overconsolidational fear
	BLOODLETTING/INJURY FEARS: An innate (mid-Paleolithic) *H. sapiens* 200,000-70,000 y/o fear circuit
"SITUATIONAL"	FEAR OF ENCLOSED SPACES: An innate (Cenozoic) simian-wide ~20,000,000 y/o fear circuit
	FEAR OF HIGH ELEVATIONS: An innate (Mesozoic) mammalian-wide ~140,000,000 y/o fear circuit
"ANIMAL"	FEAR OF DOGS, BIRDS AND BATS: A PTSD-like overconsolidational fear circuit
	FEAR OF MICE AND INSECTS: An innate (Neolithic) human ~12,000 y/o fear circuit
	FEAR OF SNAKES: An innate (Cenozoic) simian-wide ~20,000,000 y/o fear circuit

evolution of humans and dogs); 2) fear of snakes (simian-wide, thus innate for ~20,000,000 years); 3) irrational fear of insects and mice (which is Neolithic and innate for ~12,000 years). Similar inconsistencies exist in all phobia subtypes. Table 4 lists some examples. This conceptually driven article aims to produce useful cross-fertilization by interfacing research from seemingly distant scientific disciplines and different domains of knowledge. It is partly inspired by Nesse's (2001b, 2005) "Smoke-Detector Principle" of anxiety which draws from principles of financial cost–benefit analysis in economics and principles of signal detection analysis in psychophysics (Nesse, 2005, 1999; Nesse and Williams, 1994). Nesse and Williams have pointed out that fire alarms are set to produce many false positives and no false negatives because most people would rather walk down flights of stairs numerous times for a false alarm (false positive) than have a less sensitive alarm (false negative) since consequences may be grave (death by third-degree burns or by suffocation). In an attempt to obtain a similar conceptual gain by incorporating unfamiliar concepts into anxiety disorders research, the author has coined the term the "Neuroevolutionary Time-depth Principle." The principle proposed here re-clusters most DSM-IV-TR (APA, 2000) fear-related traits into four broad brain-evolution-based clusters: Mesozoic, Cenozoic, Paleolithic and Neolithic. A putative brain-evolution-based genetic architecture is outlined below as a possible target for future research (Table 3). This re-clustering of fear-circuitry-related traits is based on the Neuroevolutionary Time-depth Principle which takes into account factors such as the relative role of natural disasters and non-conspecific anthropophagic predators, versus the role of human conspecific (thus mostly non-anthropophagic) predators in driving selection of fear-circuitry-related allele variants (and possibly of relevant gene dosages) in the human genome.

5. Mesozoic (mammalian-wide) fear circuits

Mesozoic fear circuits are those that human mammals share with many other mammals. These circuits are thus posited to be hardwired in extant humans primarily by wild-type alleles driven to fixation by Mesozoic selective sweeps with no remaining allele polymorphisms (as defined by lack of allele variants with a frequency over 1%)
Neuroevolutionary Time-depth: ~140 million years (Mesozoic)

The first evolved fears to be recognized by Darwin and contemporaries were mammalian-wide. These fears have been extensively studied by evolutionary psychologists but are of no relevance to adult psychiatry. These fear circuits are observable in humans and other mammals and are considered "normal fears." These fear circuits are probably hardwired, most likely by the wild-type alleles nearing fixation in humans and most other mammals. Fear-circuits, which are posited to be hardwired by mammalian-wide wild-type alleles, include:

5.1. Normative fear of high elevations

That fear of high elevations are hardwired has been demonstrated by Gibson and Walk's (1960) visual cliff experiment, which documented that both human toddlers and day-old goats will not walk on a transparent solid surface that gives the impression of walking off a cliff (none of the experimental subjects has previously observed the consequences of falling off of a cliff, ruling out learning as the model of aquisition). Further evidence for the non-associativeness of fear of heights was found in undergraduate students (Poulton et al., 1998) and in clinical samples (Menzies and Harris, 1997; Menzies and Clarke, 1993). Unsurprisingly, it is the absence of fear of heights that is sometimes considered outside of the norm. (Interestingly, it has been widely observed that the complete absence of fear of heights such as is required of skyscraper construction worker runs in families and is difficult to acquire by non-blood relatives.)

5.2. Normative separation fears ("separation anxiety")

For a comprehensive discussion of the empirical clinical data on separation anxiety, see Kagan (1984). Bowlby (1975) has written about these fears from an evolutionary perspective. MacLean (1985) in his Triune Brain Hypothesis, pointed out that normative separation fears are the prototypical "paleo-mammalian" fears. These are the fears that placental mammals share with marsupial mammals (from which they diverged circa 130 Mya) and which do not exist in reptiles (from which all mammals diverged 140 Kya). Kagan (1984), Bowlby (1975) and MacLean (1985) focused on fears in children. In contrast, this review article exclusively focuses on fear-circuitry-related traits in adults. The author will highlight the fear circuits which are *Homo sapiens*-specific and thus, arguably, are especially clinically relevant to young, otherwise healthy adults. Key epidemiological research studies relevant to the evolution of normative separation fears (Daly and Wilson, 1988) were discussed in the Emerging empirical evidence section (above).

6. Cenozoic (simian-wide) fear circuits

Cenozoic era fear circuits are posited to be those limbic circuits that humans share with most simians (higher primates). These circuits are thus posited to be firm-wired (strongly prepotentiated) in extant humans by alleles which are the major variants in a stable polymorphism
Neuroevolutionary Time-depth: ~20 million years (Cenozoic)

Non-mammalian-wide fear circuits that humans specifically share with non-human simians (higher primates [apes and monkeys]) only began drawing interest since the publication of the landmark book by Goodall (1986), who, along with other research groups, primarily from Japan, studied African apes in their natural habitat. Recent carefully conducted studies have extended Goodall's work to some non-hominoid simians (e.g., baboons). This research, reviewed by Sapolsky (2001), suggests that many of the human fears listed below are firm-wired not only in the hominoid simians (apes), but also in non-hominoid simians (monkeys such as baboon). The relevant neuroevolutionary pressures involved arguably date back to early simian

ancestors that humans share with all other social simians (apes, gibbons and baboons).

6.1. Fear of darkness

Many predators of simians and of the Pliocene epoch (late Cenozoic era) hominins (i.e., Australopiths) were nocturnal carnivores (e.g., hyenas and jackals). Nocturnal predators, while color blind, possess excellent low-light vision. In contrast, primates (although originally evolved from rodent-like nocturnal insectivores) have subsequently evolved to be obligatory diurnals (Dawkins, 2004). Extensive research documents that, during simian evolution, a series of retina-expressed mutations that transformed some of the retina's rods into cones spread, resulting in the emergence of bi-chromatic and eventually tri-chromatic vision. The selective sweep of these retina-expressed alleles in simians is assumed to have been driven to fixation by a switch from being insectivores to being furgvores (fruit eaters). Color vision, however, came at the expense of low light vision, making fear of darkness a simian-wide fitness-enhancing trait (Dawkins, 2004).

6.2. Fear of confined spaces

Twin studies (e.g., Kendler et al., 2001) have found at least a moderate heritability of (self-reported) fear of confined spaces. This is arguably another simian-wide fear circuit because entering enclosed spaces was probably associated not only with an intrusion on a potential predator, but it also limited the option of successfully invoking the unique simian (and Pliocene hominin) flight response (arboreal escape). Furthermore, simians' forest-canopy ecological niche provided good long-distance visibility. Entering enclosed spaces diminished visibility and specifically deprived simians of their color vision advantage. It is of note that, although the human clade diverged from ancestral chimpanzees circa 5 Mya, the primary escape behavior of hominins continued to be arboreal for another 2.5 million years (Dawkins, 2004). Thus, throughout the human arboreal EEA, fear of enclosed spaces was most likely a fitness-enhancing trait.

6.3. Fear of snakes

Strong evidence for the innate nature of the fear of snakes in humans was demonstrated by twin studies discussed above (e.g., Kendler et al., 2001). Fear of snakes in rhesus monkeys was also experimentally documented by the Cook and Mineka (1989) toy snake versus toy flower study described earlier (Cook and Mineka, 1989). Arguably, the distal etiology may be related to the fact that, like simians, snakes are both terrestrial and arboreal. Thus while the arboreal flight response protected simians and Pliocene hominins (the Australopiths) from most predators, arboreality did not protect them from snakes. Primatologists have also documented that infant simians are targets of predation by snakes. Fear of snakes is very unlikely to be pan-mammalian. Some mammals (e.g., badgers) have evolved to prey on snakes. However, snake-hunting mammals are uniformly heavily furred and thus protected from snake venom. In contrast, the sparser body hair and thinner skin of many simians (notably chimpanzees and humans) probably left them much more vulnerable to snake incisors.

6.4. Fear of reptiles

A prepotentiated fear of toy reptiles (toy crocodiles) in rhesus monkeys was demonstrated by the Cook and Mineka (1989) toy crocodile versus toy rabbit experiment previously described. This simian-wide fear is most likely related to the fact that the African crocodile is a major predator of simians, and most probably also of early hominins in their indigenous East African riverine-forest ecological niche.

6.5. Fear of immersion in water (typically moving water)

The non-associative mode of acquisition of fear of water has been well-documented (Poulton et al., 1999). Furthermore, an immunization effect suggesting desensitization and eventual extinction was noted (Poulton et al., 1999). Simians including humans require desensitizing exposure to bodies of water in order to extinguish the innate fear of drowning (Poulton et al., 1999). It may be relevant in this regard that humans have spent the majority of their EEA in the riverine-forest ecological niche of the East African highlands (initially alongside small, rapidly moving, mountain streams). Drowning or being swept away by moving water was probably a frequent cause of early life mortality for most simians and early hominins. The only simian known to have evolved to seek (hot) water immersion (presumably due to very specific climate survival pressures) is the Japanese Onsen "snow" macaque of northern Japan.

6.6. Lactate-triggered acute anxiety attacks

Lactate-triggered anxiety attacks have been demonstrated in some individuals with anxiety disorders, notably including individuals with combat-related PTSD. Evolutionarily, there is no reason to expect lactate-triggered attacks to be specific to one narrow psychiatric phenotype such as panic disorder. Some speculations based on behavioral ethology may be useful in this context. Arguably, for the obligatory-terrestrial (arboreality-impaired) large mammals (e.g., zebra, antelope, eland, wildebeest, and gazelle), whose survival is dependent on outrunning large carnivores, tolerating high lactate levels from extended periods of anaerobic metabolism is critical for enabling high terrestrial speed. Neuroevolutionary reasoning thus predicts that, unlike simians, non-domesticated ungulate herbivores (such as those listed above) are less sensitive to high lactate levels. This is an easily testable/falsifiable prediction. On the other hand, in simians (including humans), metabolically costly musculature for high terrestrial speed was arguably not fitness-enhancing for two reasons: 1) their ability to invoke the simian-specific arboreal flight response (a trait which, to the best of author's knowledge, has not been documented in ungulates) and 2) the larger, metabolically more costly brain of simians. Thus, during simian evolution, high lactate levels may have been a reliable

signal of impending muscle exhaustion. More speculatively, with regard to other factors triggering acute anxiety and panic attacks in some individuals, it may be of interest that the East African Highlands are the indigenous ecological niche of both *Coffea arabica* (Ethiopia) and *Coffea robusta* (Kenya) as well as of *H. sapiens*. Arguably, the alleles for responding favorably to caffeine are thus the wild-type alleles and caffeine-sensitive individuals may possess recently mutated (possibly Neolithic) minor allele variants. More research may be warranted.

6.7. Carbon dioxide (CO_2)-triggered acute anxiety attacks

Extensive research has demonstrated that panic attacks have a non-associative mode of acquisition, and are most probably triggered by impaired orbitofrontal or mediofrontal governance over innate hardwired danger-detection circuits linking the locus ceruleus to the amygdala (Kent et al., 2005; Gorman, 2004; Amaral, 2003). Evolutionary factors in panic disorders have been proposed and are cogently articulated elsewhere (Klein, 1993, 1989, 1981). These evolutionary hypotheses are consistent with research suggesting that, unlike their prosimian ancestors, which spent rest periods in confined underground spaces with high CO_2 levels, simians, including hominins, evolved for the forest-canopy and sub-canopy ecological niche where even slight elevations in CO_2 levels were arguably reliable predictors of one of the most common Cenozoic threats to life, forest fires and forest-underbrush fires. As with lactate-triggered attacks, CO_2-triggered attacks have been demonstrated in more than one anxiety disorder, notably including combat-related PTSD. Likewise, evolutionarily, there is no reason to expect CO_2-triggered attacks to be specific to one narrow psychiatric phenotype such as panic disorder.

6.8. Acute-fear-induced jaw clenching (bite-muscle-strengthening) and chronic-stress-induced teeth grinding (incisor-sharpening)

Fear-induced jaw clenching and gnashing, as well as incisor-sharpening (bruxing), is widely documented in most simians (Sapolsky, 2001, p. 104). The ability to invoke a lethal bite may have been a highly conserved trait during primate evolution since members of the order Primata lost their sharp claws in the process of evolving long prehensile fingers (to a lesser degree, this is also true for the order Rodentia, the order closest to the Primate order). As we have argued elsewhere (Bracha et al., 2005e), most simians (and presumably Pliocene *Australopiths* and early-Paleolithic *Ergasts*) were probably highly dependent on a lethal bite during close combat with conspecifics. The simian-wide phenomena of fear-induced bite-muscle-strengthening (jaw clenching, gnashing) and incisor-sharpening (teeth grinding, bruxing) have been widely observed in fear circuitry disorders clinics, such as PTSD clinics. For further discussion of possible clinical implications of PTSD, see sub-section below (neuroevolution-based contributions for the forthcoming refinement of the Department of Veterans Affairs compensation and pension examination and for the forthcoming revision of PTSD Criterion-D in DSM-V).

7. *H. sapiens*-specific fear circuits

These are *H. sapiens* fear circuits posited not to have existed in the early Paleolithic genus *Homo* (*H. ergaster*). It is posited that these circuits are thus firm-wired in a small percentage of extant humans primarily by common minor alleles which spread from single ancestral copies either during the mid Paleolithic (i.e., pre-*FOXP2*) or in the upper Paleolithic (i.e., post-*FOXP2*) EEA, in both cases primarily driven by mate-choice-related stabilizing selection

Neuroevolutionary Time-depths (*H. sapiens*):
~200 Kya to ~70 Kya (mid Paleolithic)
and ~70 Kya to ~12 Kya (upper Paleolithic)

The neuroevolutionary insights into mid and upper Paleolithic (thus human-species-specific) fear circuits have received limited attention from previous theorists, but the author argues that these are especially relevant to research on clinical stress-triggered and fear circuitry disorders. These *H. sapiens*-specific fear-circuitry-related genomic changes are the focus of this conceptually driven review. The author proposes that these can be divided into two groups which are tentatively termed: pre-*FOXP2* (mid Paleolithic) mutations, and post-*FOXP2* (upper Paleolithic) mutations. These phylogenomic terms are used here with the understanding that *FOXP2* is only one of several brain-expressed mutations that appeared (possibly in short sequence) at the transition between the mid and upper Paleolithic (Zhang et al., 2002). The pre-*FOXP2* group is probably smaller than the post-*FOXP2* group and only one example of a pre-*FOXP2* fear-circuit-related mutation will be given below.

7.1. The pre-FOXP2 hypothesis of irrational bloodletting/injury fears (the pre-speech Paleolithic-threat-hypothesis of blood injection injury phobia)

The Paleolithic threat hypothesis of irrational bloodletting fears presented in several recent articles (Bracha et al., 2005a; Bracha, 2004; Bracha et al., in press) posits that a balanced (stable) allele polymorphism predisposes some individuals to fear-triggered efferent vasovagal faints that entered the human genome via mate-choice-driven stabilizing selection in the mid Paleolithic EEA, the last preverbal (pre-*FOXP2*) stage of the *H. sapiens* EEA. The mid Paleolithic is the period during which anatomically and mitochondrially modern humans evolved into neurally modern and articulated speech-enabled humans, presumably because of a selective sweep by several brain-expressed mutations of moderate or large effect (Klein and Edgar, 2002). One of these is probably the mutation that produced the modern *FOXP2* locus, which has recently been shown to exist in a different form in *P. troglodytes* (CSAC, 2005). Furthermore, analysis of the *FOXP2* DNA sequence indicates that it has very low sequence diversity in extant humans suggesting a relatively recent selective sweep that took place after the appearance of *H. sapiens* circa 200 Kya (Hill and Walsh, 2005). Mutations in the *FOXP2* have been identified as the cause of a syndrome which exists in a single three-generation pedigree in which a severe speech and language disorder is transmitted as an autosomal dominant monogenic

trait. This language impairment is part of a broader syndrome which includes impairment in speech comprehension, articulation, a praxic deficit that involves non-linguistic mandibular movements (brain size, however, is normal). Studies of FOXP2 locus indicate that this disorder is a consequence of haploinsufficiency during embryological development and that the phenotype results from a reduction in gene dosage (Nokelainen and Flint, 2002). The emerging consensus in paleoanthropology is that this monogenic linguistic and articulation impairment existed not only in *H. neaderthalis* from which *H. sapiens* diverged circa 450 Kya, but also in mid Paleolithic archaic *H. sapiens* (200 Kya to 70 Kya). The paleoanthropological consensus is that the mid Paleolithic archaic *H. sapiens* was restricted to using sign language and probably had great difficulties understanding future tense and past tense. The mid Paleolithic archaic *H. sapiens* was fully anatomically modern, strongly suggesting that they possessed the modern wild-type *ASPM* and *microcephalin* genes. However, since speech emerged rather abruptly circa 70 Kya, it is likely that the advantageous *FOXP2* mutation was among those which enabled the transition from the mid Paleolithic to the upper Paleolithic. As we have argued elsewhere (Bracha, 2004; Bracha et al., 2005a), fear-induced fainting is highly likely to be part of the extensive sign language that humans needed during the mid Paleolithic in order to survive inter-group conflict. As we have previously argued, during mid Paleolithic periods of inter-group bloodshed, fear-induced faints served the function of visually (non-verbally, "non-*FOXP2*-ally") signaling to raiding conspecifics that one does not present a danger, thus increasing the odds of survival for a fainting-prone non-combatant. This hypothesis is the only one to the author's knowledge that can explain the age and sex pattern of bloodletting/injury fears (and of its overlapping conditions known under a wide variety of names: psychogenic fainting, the emotion-triggered "common faint," efferent-vasovagal fainting, neurogenic fainting, neurally mediated syncope, pseudocardiogenic fainting and neurovascular fainting). A large, landmark epidemiological study of blood injection injury fears (1920 subjects in the Baltimore ECA study) found an overall female-to-male ratio of 2.4:1 (Bienvenu and Eaton, 1998). The hypothesis that the anthropogenomic origins of blood-injection-injury fears are not earlier than the mid Paleolithic are also consistent with the extensive evidence of widespread habitual nutritional intra-hominin anthropophagi (human cannibalism) which was practiced by early Paleolithic Ergasts. Thus, fainting at the sight of bloodshed-related stimuli is unlikely to be of greater time-depth than the mid Paleolithic. Arguably, the archaic *H. sapiens* male, which emerged only 200 Kya, was the first predator for whom some humans (primarily young women) were more valuable alive than dead. Others have made similar observations with regard to peritraumatic dissociation (Perry et al., 1995). Finally, as many authorities have noted, evolution is "blind," and not forward-looking (Cosmides and Tooby, 1992). In this context, human brain evolution could not "anticipate" a future environment in which having a sharp object penetrate one's skin or seeing one's blood could be anything but dangerous. Epidemiological data in support of the mid Paleolithic threat hypothesis of bloodletting-related fears are accumulating (Bracha, Bienvenu, and Eaton, submitted for publication).

Two of the many additional predictions based on this hypothesis are:

1. In the immediate aftermath of intentionally caused disasters, such as terrorism against civilians, epidemics of pseudo-cardiological fear-induced fainting are to be expected (Bracha et al., 2005a,c).
2. One of the "phobia subtype-specific" (Kendler et al., 2001) loci involved in bloodletting/injury fears may carry a developmentally sensitive gene (existing in a stable polymorphism) in which the expression mechanism is gradually suppressed by pleiotropic androgens such as dehydroxyepiandrosterone sulfate (DHEA-S) and testosterone. This is likely to manifest as a decrease in gene penetrance following puberty in males (and possibly following menopause in females). The pleiotropic adrenal-cortical androgen DHEA-S is especially intriguing as a possible pre-blood-drawing intervention for bloodletting fears, because, unlike testosterone which decreases, DHEA-S normally increases during extreme fear (Morgan et al., 2004). A testable hypothesis is that a brief DHEA-S course prior to blood drawing may be beneficial for susceptible individuals.

Consistent with the *H. sapiens*-specific hypothesis of blood injection phobia presented above, fright-induced fainting is not uniformly fitness-enhancing, and accordingly, has not been reported when the threat is from natural disasters such as forest fires, floods, volcanic eruptions, pandemics or a threat from anthropophagic predators.

7.2. Fear circuits posited to be wired by Paleolithic mutations which are post-FOXP2 (upper Paleolithic)

Compulsive lock checking
Compulsive stove checking
Compulsive cleaning and obsessive fear of contamination
Compulsive hoarding (especially of tools, weapons, foot coverings and leather goods)
Extreme fear of insects or mice
Fear of simultaneous visual scrutiny by adult non-kin conspecifics (Generalized Social Phobia).

7.3. Compulsive lock checking (entry barrier checking) and stove checking (hearth checking) behaviors

Checking behaviors have long been intuitively understood as pathological tails (high gene dosage-driven?) of fitness-enhancing fear circuitry behaviors. The heritability of obsessive-compulsive traits such as compulsive checking is demonstrated by twin studies (Jonnal et al., 2000). Evolutionarily, compulsive entry-barrier checking most likely became a fitness-enhancing trait when humans began establishing semi-permanent settlements in the upper Paleolithic. Among upper Paleolithic humans, fear of a surprise

attack by a predator, either conspecific or non-conspecific, was nearly constant. Similarly, compulsive checking of stoves is likely a conserved hearth checking behavior. Finally, some comorbidities between severe checking behaviors and paranoid traits (but not other psychotic symptoms) would be predicted by neuroevolutionary reasoning. This is another testable prediction.

7.4. Compulsive washing, compulsive cleaning and obsessive fear of contamination

Fears of contamination are also intuitively understood as the pathological tail of an evolved fitness-enhancing fear circuit. Evolutionarily, "fear of public bathrooms," which in some studies is lumped with Generalized Social Phobia, may be better classified as part of OCD as fear of contamination. Although no research data are available, arguably, these patients experience intense disgust rather than "fear" in proximity to human-excrement-related stimuli (disgust circuits may be quite different from fear circuits). Human excrement unquestionably became a major factor contributing to epidemics beginning in the upper Paleolithic. An experimentally testable prediction, which follows from the above neuroevolutionary reasoning, is that, since infections are less easily transmitted from animals to humans, patients with "fear of public bathrooms" will be much less disturbed by the sight/odor of excrement of other species (e.g., rabbits or dogs) than the sight/odor of human excrement. A possible objection to the hypothesis that compulsive grooming/cleaning is of upper Paleolithic time-depth is that paw licking in some inbred domesticated canids suggests that these compulsive behaviors have a mammalian time-depth. However, the prevalence of compulsive behaviors in dogs is much lower than in humans. It is thus possible that cleanliness has been intentionally selected into the dog genome by human breeders only in the last few hundred years. Furthermore, little known paleo-archaeological research on upper Paleolithic garbage pits (middens) may be relevant in this regard (for recent reviews, see Tattersall, 1998; Brothwell and Brothwell, 1998). Paleo-archaeological research strongly suggests that the domestication of wolves into dogs occurred when orphaned wolf pups began scavenging animal bones from upper Paleolithic middens and consequently became imprinted on humans (Brothwell and Brothwell, 1998). The trait of paw licking may have been selected into the genome of some dogs because of the 15,000-year-long exposure to human middens. Arguably, pups with stronger grooming habits better survived the continuous exposure to infectious human waste. A falsifiable prediction which follows from the above reasoning is that paw licking and other over-grooming behaviors will not be found in undomesticated canids such as hyenas, jackals or wolves.

7.5. Male-pattern compulsive hoarding versus female-pattern compulsive hoarding

Until the beginning of the upper Paleolithic, human foragers could only own what they could carry (on either side of their skin, i.e., as subcutaneous fat or on their person). In contrast, in the upper Paleolithic, humans became increasingly settled and food hoarding has long been understood as a behavioral trait that evolved in response to upper Paleolithic nutritional stress. The author posits that a much-neglected factor in the evolution of compulsive hoarding was upper Paleolithic warfare. Human inter-group warfare was nearly constant beginning in the upper Paleolithic (see Keeley, 1996; LeBlanc and Register, 2003 for comprehensive reviews). Evidence for hoarding of non-food items in the upper Paleolithic is extensive. In particular, inordinately large hoards of unused stone axes (which served as both tools and weapons) have been documented (Tattersall, 1998 pp. 139). Also see LeBlanc and Register (2003) for a review. The paleoanthropological data lead to the prediction that extant males with compulsive hoarding traits will primarily hoard tools and/or weapons. It is especially noteworthy that, unlike most fear-circuitry-driven behaviors, hoarding is *more* common in males than in females (the only other anxiety disorder with this unique sex ratio is severe clinical social phobia, as briefly discussed below). In the groundbreaking Johns-Hopkins study of 126 subjects with OCD, nearly 30% of the subjects had hoarding symptoms, and hoarding was *twice* as prevalent in males than females (Samuels et al., 2002). Importantly, Samuels et al. (2002) suggest that hoarding appears to be transmitted in some OCD families and may differentiate a clinical subgroup of OCD (a conclusion consistent with a growing literature supporting the heterogenous nature of OCD). The unusual male to female ratio (2:1) reported by the Johns-Hopkins group is consistent with neuroevolutionary theory. Hoarding by upper Paleolithic males (presumably of tools and weapons) was arguably more fitness-enhancing than hoarding by females (presumably mostly of food items) since, in the Paleolithic, food storages were vulnerable to rodents, insects, or spoilage (i.e., to fungi and bacteria), or to theft by hostile conspecifics. Weapons, on the other hand, could have been used to protect food storages as well as for obtaining food by raiding neighboring groups during periods of nutritional stress (Keeley, 1997). A very different pattern of non-food-item hoarding is neuroevolutionarily predicted in extant females. It is posited that an important fitness-enhancing trait among upper Paleolithic females was hoarding of two survival-enhancing items: first, leather foot-coverings for extended forest foraging (boots/shoes), and second, leather containers for transporting gathered foods (bags). It may be of interest that, during foraging as well as during long-distance migrations, Paleolithic females are believed to have carried two under-arm leather bags: one containing fat/protein-rich foods and the second carrying the unweaned infant. This under-arm positioning of bags facilitated breastfeeding while mobile and easy access to the above high-energy foods. Since leather deteriorates rapidly in the ground, at present, there are no paleo-archaeological data in support of this speculation. However, ongoing paleo-archaeological digs in the Northern Eurasian permafrost (where leather remains intact) may be able to test this and related predictions. More importantly, the

predicted sex differences in hoarding patterns discussed above are easily testable in extant humans. Two intriguing (and clinically important) studies by Freeman et al. (1994, 2003) demonstrate that hoarding patterns can be studied even in severely ill clinical populations. Unfortunately, their data do not inform the issue at hand since all the subjects were combat-exposed veterans. Further research on hoarding patterns using random samples and warzone-unexposed OCD patients is needed. Finally, on a highly speculative note, evolutionary reasoning predicts that both the male-pattern hoarding (tools/weapons) and the female-pattern hoarding (shoes/under-arm bags) will be most pronounced in individuals whose geographic ancestry is in regions where foraging (a.k.a. hunting/fishing/gathering) subsistence ended most recently (northern Eurasia, the British Isles, and Japan). One of several epidemiological testable predictions that follows from the above is that significantly higher national consumption of the above hunting/gathering linked consumer goods would be found in high-per-capita-income world regions in which foraging subsistence ended first (e.g., Kuwait, Bahrain, Qatar, the United Arab Emirates, and Singapore) compared to world regions with similarly high-per-capita income in which foraging subsistence ended last (e.g., Japan and Scandinavia). The above hypothesis can also be tested in clinical populations. Elsewhere (also see below) we have argued that, for other evolutionary reasons, acute pseudoneurological manifestations of anxiety will have a higher prevalence in the above world regions in which hunting/gathering subsistence ended *first* (Bracha et al., 2005c).

7.6. Irrational fear of all insects

Most prosimians and simians feed on termites and other insects, and extensive research (e.g., coprolite studies) has documented that early hominins also fed on a wide variety of insects (Brothwell and Brothwell, 1998). However, the fear of insects arguably became a fitness-enhancing trait in the upper Paleolithic, once humans established settlements. It has been documented that the proximity of humans, insects and garbage middens made insects significant vectors of disease in the upper Paleolithic (Brothwell and Brothwell, 1998). In Kendler et al.'s (2002) large twin study of 64 subjects with "bug phobia," 40.6% reported "trauma to self" as the mode of acquisition. On the other hand, a full 43.8% of subjects with "bug phobia" reported "no memory" of any such trauma. Kendler et al. (2002) conclude that their findings are consistent with the evolutionary etiology of insect phobia.

7.7. Irrational fear of smaller murids (mice)

Unlike fear of rats, fear of mice among extant humans is irrational (and thus included in most large studies of specific phobias). The threat that mice posed to food storages in the upper Paleolithic arguably made a panic response at the sight of mice a fitness-enhancing trait. Additionally, paralleling the pattern with insects, mice likely became a major vector of disease only after the establishment of settled communities in the upper Paleolithic.

7.8. Irrational fear of simultaneous visual scrutiny by non-smiling, non-kin conspecifics (social-anxiety-related traits)

Social phobia and agoraphobia are the only two phobias in which Kendler et al. (2001) found that family environment may have an impact on risk. Nevertheless, moderate heritability of social anxiety traits was demonstrated in the same study (Kendler et al., 2001). A conceptually driven landmark genomic study has documented an association between social anxiety traits and an (balanced) allele-variant polymorphism in the Beta-1 adrenergic receptor (Stein et al., 2004). Evolutionary factors contributing to social anxiety traits are cogently articulated elsewhere (Stein, 1998; Stein and Bouwer, 1997; Stein et al., 1996). Several authorities have argued that, during parts of the human EEA, being stared at by a large group of strangers was frequently associated with potential threat to life. Stated differently, for upper Paleolithic *H. sapiens*, situations in which an individual was simultaneously scrutinized by a large group of non-smiling, non-kin conspecifics were more likely than not to be followed by negative consequences. This neuroevolutionary hypothesis can be tested empirically in patients with social-phobia-related traits (e.g., by comparing autonomic nervous system response and neuroendocrine response during visual scrutiny by a large group of non-kin versus a comparably sized group of blood relatives). Previous studies and the DSM-IV-TR cluster together two innate fears of arguably different time-depths as "social-anxiety-related traits": 1) a generalized fear of "new people" — an innate upper Paleolithic ~70,000 y/o fear of non-blood-related conspecifics and 2) fear of public bathrooms — an innate Neolithic ~12,000 y/o fear of fecal contamination. Arguably, this clustering is unhelpful in charting the genetic architecture of social-anxiety-related traits. Finally, it may be of note that, with regard to the sex ratio of anxiety disorders, men are generally believed to under-report symptoms of most phobic and anxiety disorders in both epidemiological and clinical studies. Male under-reporting may partly account for the typical sex ratio of anxiety disorders. In contrast, objectively severe social anxiety (severe enough to require hospitalization) presents primarily in males (DSM-IV-TR, 2000, p. 453). In this regard, the sex ratio of severe social phobia (as well as of severe OCD) stands out among anxiety disorders. The high prevalence of clinically significant social anxiety among males is consistent with neuroevolutionary predictions since, in the mid–upper Paleolithic EEA, visual scrutiny by a large group of strangers was more likely to result in loss of life for a male than for a female. Goodall's (1986) research on the patterns of behavior of the chimpanzees of Gombe leads us to predict that, especially in males, symptom severity during meeting "new people" will often manifest only when the "new people" encountered include three or more men. This prediction can be easily confirmed or disconfirmed in clinical samples.

8. Neolithic-culture-bound species-*atypical* fear circuits in extant culture-bound genomes (gene–culture co-evolution)

These are species-*atypical* (psychopathological) fear circuits which are posited to have been firm-wired (prepotentiated) in a small number of extant humans by previously rare allele variants. It is likely that these allele variants spread only after the emergence of human Neolithic tribalism (cultures) and mostly by gene–culture co-evolution and by mate-choice-driven stabilizing selection
Neuroevolutionary Time-depth: ~12 Kya (Neolithic)

Neuroevolutionary insights into fear circuits of Neolithic time-depth have received little attention until recently and, to the best of the author's knowledge, were first introduced in a recent article (Bracha et al., 2005a,b,c,d,e). The author argued that these are highly relevant to clinical research on some of the most puzzling fear-triggered syndromes such as acute "conversive" symptoms. They may also be relevant to clinical research on fear circuitry disorders which DSM-IV-TR considers "culture-bound" (further discussed later in this article).

8.1. Molecular phylogenetics of the lactase messenger RNA transcription-controller-gene: implications for Pseudo-neurological "conversion" disorder

It may not be immediately obvious that the Neolithic time-depth (circa 480 generations) is of sufficient evolutionary duration for the establishment of allele variant polymorphism via a stabilizing selection. However, the now classic molecular genetic studies of the hereditary persistence of intestinal lactase (HPIL) minor allele variant (i.e., the allele for digesting lactose past age four) are illuminating in this regard. A mutation causing inactivation of the transcription-controller-gene (TCG) that originally suppressed transcription of lactase mRNA at age four permitted consumption of large amounts of fresh milk. This lactase messenger RNA TCG mutation spread (from a Paleolithic single ancestral copy) only in the Neolithic and was probably driven by the domestication of ovine, bovine and other ungulate herbivores. The TCG mutation facilitated the emergence of pastoralism and the subsequent Neolithic expansion into previously uninhabited ecologically harsh regions of Asia (Cavalli-Sforza et al., 1994). A similar pattern has been documented in Europe during Neolithic expansion into the previously uninhabited Scandinavia. These studies of HPIL have shown that as little as 60 generations were sufficient for the single loss-of-function mutation (which disabled the lactase mRNA transcription-controller-gene) to increase over 90-fold (OMIM, 2004; Hollox et al., 2001; Harvey et al., 1998; Holden and Mace, 1997; Cavalli-Sforza et al., 1994). Prior to the Neolithic domestication of ungulate herbivores, a trait enabling humans to digest fresh milk past the age of four would have allowed foraging-capable individuals to compete with their unweaned blood relatives for human breast milk during periods of nutritional stress. Competition with unweaned blood relatives for breast milk would have reduced the Paleolithic milk-digesters' inclusive fitness. It is of note that the allele enabling adult humans to digest milk remains the minor allele variant in the global stable polymorphism. (Thus, the majority of extant humans cannot digest milk past age four and obtain calcium primarily from powdered fish bones.) Another relevant insight from the research on HPIL is that alleles over time often rapidly change back and forth between being harmful, then helpful, then harmful again. The allele for digesting milk in adulthood, which first turned helpful in the Neolithic expansion, turned harmful again when humans began living past their reproductive years and became vulnerable to atherosclerosis (Harvey et al., 1998). Even more relevant in the context of this article is the landmark study by Mekel-Bobrov et al. (2005) cited above which provides evidence that important brain-expressed genes such as the ASPM can also undergo rapid evolution well within the Neolithic time-depth (5800 years).

8.2. Fear-triggered pseudo-localized symptoms (pseudoneurological "conversion" symptoms): Neolithic-time-depth fear of being mistaken for a combatant?

The above HPIL and ASPM studies demonstrating that the Neolithic EEA was of sufficient time-depth to allow gene–culture co-evolution-based allele-variant polymorphism to be established by balancing/stabilizing selection, are highly relevant to pseudoneurological (a.k.a. conversive) disorders (Bracha et al., 2005c). There has been almost no previous discussion of neuroevolutionary factors in the etiology of the pseudoneurological (pseudo-localized) symptoms which appear during and in the immediate aftermath of inescapable stress. As others and we have pointed out elsewhere, in light of the increasing threat of terrorist attacks against civilians, more attention is warranted to acute pseudoneurological (pseudo-localized) symptoms. Additionally, more attention is warranted to epidemic sociogenic symptoms (previously known as mass hysteria) which emerge in the immediate aftermath of large-scale disasters, especially intentionally caused disasters (Bracha et al., 2005c; Bartholomew and Wessely, 2002; Wessely, 2000). We have recently proposed that a firm-wired fear circuitry response resembling a severe handicap, such as pseudo-paralysis (limping), pseudo-cerebellar symptoms (staggering, astasia abasia), psychogenic loss of sight, or falling to the ground with convulsion-like paroxysms (psychogenic non-epileptic attacks, pseudo-seizures), was selected into some genotypes, specifically during the Neolithic, resulting in a balanced (stable) allele variant polymorphism (Bracha et al., 2005c; Cavalli-Sforza et al., 1994). During Neolithic periods of warfare, acute pseudoneurological symptoms may have provided a non-verbal message to predatory conspecifics (often raiders from a tribe that spoke a different language) that one is unlikely to be an immediate threat because one is severely injured or severely diseased (even, possibly infectious with an agent that the raiders immune system has not previously encountered?) (Bracha et al., 2005a). This is consistent with the age and sex pattern of conversive disorders (Boss, 1997). LeBlanc and Register (2003) reviewed warfare patterns of Neolithic New Guinea cultures and reported that 25% of men,

but only about 5% of women, are killed during warfare (p. 151). Similar numbers were reported in studies of other Neolithic cultures (Keeley, 1996, p. 196). Also see Keeley (1997) and Ferguson (1997). The hypothesis that pseudoneurological symptoms are of recent (Neolithic) time-depth is also evinced by the observation that the predisposing alleles were not driven to fixation but rather remained species-*atypical*. It is especially of note that the molecular phylogenomic techniques developed in Mekel-Bobrov et al.'s (2005) study on the mid-Neolithic (5800 YA) adaptive evolution of *ASPM* can easily be applied to the Neolithic Time-depth hypothesis regarding the genetic factors contributing to the spectrum of symptoms still often conceptualized in Freudian terms and presently known by the psychoanalytic term "conversion disorder", in DSM-IV-TR (APA, 2000). Elsewhere, Bracha et al. (2005c) present six falsifiable predictions and possible taxonomic implications for the forthcoming DSM-V (Kupfer et al., 2002) and for the next edition of the International Classification of Disease (ICD, 2005). For a discussion of other anxiety disorders which are posited to be of Neolithic time-depth, see section below titled: Towards a science-based DSM-V reconceptualization of anxiety disorders which DSM-IV-TR currently labels as 'culture-bound'.

8.3. The ICD-10 (and DSM-V) Dissociative-Conversive Spectrum

ICD-10 (WHO, 1992) has re-categorized conversive disorders as part of the dissociative spectrum, coining the term "Dissociative-Conversive Spectrum." In a recent review, Bracha et al. (2005e) have argued, based on Perry et al.'s (1995) paper on dissociative symptoms, that the evolutionary hypothesis presented above for pseudoneurological syndromes is highly consistent with dissociation and conversion constituting a continuous spectrum as in the ICD-10 (and hopefully in the DSM-V). We have argued that some psychogenic dissociative symptoms can be conceptualized as the less severe and therefore more common variant phenotype of the Dissociative-Conversive Spectrum. Dissociative symptoms are increasingly believed to be a manifestation of various hyper-glutamatergic states. These hyper-glutamatergic states are most often stress-induced, but as we argued elsewhere (Bracha and Chronicle, 2006), some may be occassionally of other etiologies, such as supra physiological glutamate levels in the diet. Furthermore, extensive research by the West-Haven V.A. (Chambers et al., 1999; Anand et al., 2000; Morgan et al., 2003) strongly suggests that dissociative symptoms may respond to glutamate release inhibitors such as lamotrigine. A clinically relevant testable prediction that follows from the continuity between dissociation and conversion is that various forms of pseudoneurological conversive symptoms may also respond to lamotrigine or other glutamate release inhibitors, especially when used at higher doses. Finally, if conversion and dissociation represent a severity continuum or variant phenotypes, it is likely that dissociative traits can be traced to fear circuits of the same time-depth as the pseudo-localized (conversive) symptoms (i.e., Neolithic time-depth).

9. Resilience to warzone-related PTSD: testable predictions and speculations based on the neuroevolutionary time-depth principle

Andreasen (2004), in a recent editorial about "The stress symptoms that we refer to as PTSD and ASD," has argued that DSM-V should rethink the conceptualization of the above spectrum of symptoms. Remarkable breakthroughs have been made in understanding ontogenetic and other proximate factors in the etiology of the syndrome currently known as PTSD. However, there has been little attention to possible distal factors (Silove, 1998). In this article, space limitations do not permit extensive discussion of possible neuroevolutionary contributions to a DSM-V reconceptualization of PTSD. However, a few examples of the possible explanatory power of neuroevolutionary insights are provided below.

9.1. Resilience following different Criterion-A adversities (events): insights from the time-depth principle

A widely replicated but neurobiologically unexplained finding is that different types of Criterion-A adversities (currently known as "events") have very dissimilar rates of subsequent PTSD. For example, in the NCS (Kessler et al., 1995, 1994), resilience following fires was found to be high and no significant sex differences were found (PTSD developed in 4% of exposed males and 5% of exposed females). In contrast, the NCS found much lower resilience to combat and to physical abuse, (subsequent PTSD was found to be 39% and 22%, respectively). Research has not yet fully explained why fires are five to ten times *less* likely to result in PTSD than physical abuse or combat. The lower rates of PTSD following fires require explanation since, of the above three Criterion-A adversities, it is arguably death in a fire (loss of life by third-degree burns or by suffocation) that is the most dreaded. Table 5 below presents some speculations regarding the much lower subsequent rate of PTSD following natural adversities (e.g., forest fires). As very briefly summarized in Table 5, there may be a direct positive correlation between neuroevolutionary time-depths and the degree of stress resilience. It is posited that adversities such as forest fires, for which the human genome had at least 140,000,000 years to evolve, are less likely to result in PTSD than adversities for which the human genome has had a much shorter time to evolve. There are several valid critiques of this hypothesis, such as the subjective nature of self-report, but this hypothesis is falsifiable and these valid critiques are amenable to research. Another testable hypothesis is that, although death by drowning in a flood is arguably more dreaded than death by being shot, PTSD rates in the aftermath of floods of unprecedented size, such as those following hurricane Katrina, will be lower than those seen after warzone exposure. These rates may be more in line with those following forest fires (in the single digits).

9.2. Avoidance coping of PTSD adversity reminders: a role in the Neolithic demic expansion?

Until recently, it was widely assumed that, throughout human prehistory, practically all demic expansions (population

Table 5
Differential resilience to PTSD following different types of Criterion-A events: possible insights from the neuroevolutionary-time-depth principle

NCS term for the particular fear-circuitry-activating threat	Rates of subsequent lifetime PTSD in exposed extant humans (NCS data)	Posited relevant criterion-A adversity during the relevant part of the human EEA	Time-depth (years) available for the human genome to evolve resiliency to the specific criterion-A adversity	Posited frequencies of resilience-related alleles
"Fire"	4% (M) 5% (F)	Natural disasters (most frequently forest fires) in the presence of which terrestrial mammals *of both sexes* were exposed throughout their evolution	140,000,000 since the emergence of mammals in the Mesozoic	Very high (resilience-related alleles are probably the species typical wild type alleles in humans, and approaching fixation)
"Physical child-abuse" (boys) (essentially, the physical abuse of stepsons)	22% (M)	*Intra*-group male-male violence against non-blood-related younger male simians *in the same troop* ("stepchildren") is well documented in most simian species studied (e.g. baboons, chimpanzees, and gorillas)	20,000,000 since the emergence of social simians in the Cenozoic	Intermediate
"Combat"	39% (M)	*Inter*-group male-male Intra-human killings (large-scale inter-ethnic battlefield warfare) only became common after the rising of population densities in the Neolithic.	12,000 since the emergence of tribalism (a.k.a "ethnic identity") in the Neolithic	Low (resilience-related alleles are probably the minor alleles)

Approximate evolutionary time-depths available for the human genome to select resiliency alleles for different criterion-A adversities. Epidemiological data cited from the National Comorbidity Study (NCS) (Kessler et al., 1995). Time-depth approximation based on Dawkins (2004).

migrations) were driven exclusively by the search for new material resources. However, Cavalli-Sforza et al. (1994) have demonstrated that nutritional-stress-driven Neolithic demic expansion progressed on average at a rate of only 1 km per generation. The well documented, sudden long-distance Neolithic demic migrations (e.g., across deserts, through icy mountain passes or to distant islands) are harder to explain merely as a search for material resources. For example, as Jared Diamond (2005) points out in his extensive discussion of the Polynesian Neolithic expansion, "the thought of a several-day canoe voyage across open ocean [is] intolerable to me, something that only a desperate need to save my life could induce me to undertake" (p. 130). Based on recent reviews (LeBlanc and Register, 2003; Keeley, 1996; Diamond, 2005), it is posited here that adversity reminders played a major role in the long-distance Neolithic expansion. Individuals with highly overconsolidated trauma-memory purposely migrated long-distances in search not only of safety but also of visually dissimilar landscapes which triggered fewer trauma reminders (avoidance coping). Similar PTSD-based factors may have also played a role in some earlier documented long distance migrations e.g., across the Alps, the Khyber Pass (Oppenheimer, 2003) and across Wallace's Line (the Java, Bali, Lombok, Sumbawa, Flores crossing).

9.3. Suboptimal dosages of harm-avoidance-related genes, and subsequent self selected warzone exposure

A second major contribution by Nesse and Marks has been to point out numerous modern (non-EEA) threats to life that are insufficiently anxiogenic (e.g., guns, reckless driving, or crossing busy streets). The time-depth of such threats is extremely short, usually less than a few hundred years. These authors have coined the term "hypophobias" (Marks and Nesse, 1997). There may be some implications of the hypophobia concept to combat-related PTSD. Low-harm-avoidance individuals are over-represented among those who enlist into a full-time-active-duty warfighter career. Stein et al.'s (2002) twin study has demonstrated that exposure to assaultative trauma is not random, and that additive genetic effects explained part of the variance in exposure to assaultative trauma. Stein et al.'s twin studies are also consistent with the earlier twin studies in military veterans by Lyons et al. (1993) as well as the twin studies by True et al. (1993) which demonstrated low heritability of combat-related PTSD (i.e., compared to most specific phobias, panic disorder, bipolar disorder, schizophrenia and autism). True et al. found that:

> "…after adjusting for differences in combat exposure; genetic factors account for 13% to 30% of the variance in liability for symptoms in the reexperiencing cluster, 30% to 34% for symptoms in the avoidance cluster, and 28% to 32% for symptoms in the arousal cluster."

That the avoidance and arousal clusters may be more heritable than reexperiencing is not surprising. (True et al. also concluded that there is no evidence that shared environment contributes to the development of PTSD symptoms.) It may be relevant in this context that this relatively low heritability of PTSD is in the same range as the heritability of being infected with tuberculosis (Comstock, 1978; Bracha, 1986), a disorder which, like PTSD (but unlike most anxiety disorders), obviously requires a major unique environment etiological component.

The above twin studies suggest that the etiological complexity of combat-related PTSD may be partly due to it being an overconsolidational fear circuitry overactivity superimposed on a premorbid suboptimal dosage of harm-avoidance-related genes. Since most anxiety disorders probably require a supra-optimal dosage (or over-expression) of these harm-avoidance genes, in DSM-V, a new category of "overconsolidational spectrum disorders", anchored around PTSD, may need to be created and conceptualized as straddling (and Venn-

diagramming with) the fear circuitry spectrum disorders category (Charney et al., 2002) and the affective spectrum disorders category (Hudson and Pope, 1990; Hudson et al., 2003, 2004). That PTSD may be as akin to the affective spectrum disorders as it is to fear circuitry disorders is consistent with the conclusions of Yehuda et al. (1998). These authors have reviewed two large, carefully conducted studies on the response to a Criterion-A event (terrorist attack and motor vehicle accident), and concluded that major depression alone and an anxiety disorder alone were approximately as common as PTSD following the Criterion-A event.

Classifying psychiatric disorders somewhat categorically, although unhelpful in research, is a clinical necessity and will exist in DSM-V. Arguably, a new DSM-V category of "Overconsolidational Disorders," anchored around PTSD, may be helpful since it can guide early prevention and treatment. For example, Friedman and Harris have cogently noted (Friedman and Harris, 2004) that a potential "morning after pill" may be available for the prevention of PTSD (and related post-disaster disorders) in the form of Pitman's secondary-prevention propranolol protocol (Pitman et al., 2002; Vaiva et al., 2003). Such a "morning after" prevention regimen may then be specifically indicated for all over-consolidational disorders and possibly in post disaster situations based on an individual's heart rate (tachycardia).

Finally, it is, of course, highly likely that the over-expression, or "high-normal" expression, of otherwise fitness-enhancing common "good memory alleles" (F>m) may also be a risk factor for overconsolidational disorders, especially among civilians diagnosed with PTSD. Arguably, these are the patients for whom a brief "therapeutic forgetting" protocol can be beneficial (and eventually specifically indicated, in lieu of the current, more lengthy psychological interventions).

9.4. 21st century warfare versus firm-wired limbic circuits for Neolithic warfare patterns

21st century warfighters are expected to endure warzone exposure usually lasting 6 to 12 months. Such chronic activation of a warrior's locus coeruleus to amygdala circuit did not exist during the EEA since actual combat during the EEA usually lasted only hours or at most a few days. For winning war parties, operational-combat stress were probably followed immediately by several days of high-vagal-tone recuperative behaviors consisting of resting, sleeping, feasting, and other forms of prehistoric male recreation. Bio-anthropological studies have documented this very specific pattern of prehistoric inter-group warfare in the Neolithic and upper Paleolithic. These patterns have been confirmed by several paleogenomic and gene-flow studies of male lineages through the Y-chromosome and of female lineages and female migration patterns through mitochondrial DNA (Underhill et al., 2001; Seielstad et al., 1998). These studies have also found that, in contrast to the total war patterns of the 20th century CE (and the urban warfare characterizing the early years of the 21st century), inter-group warfare in the upper Paleolithic and Neolithic EEA almost exclusively involved raiding parties of young, mate-less post-pubertal males primarily in search of reproductive resources (LeBlanc and Register, 2003; Larsen, 1999; Maschner and Reedy-Maschner, 1998; Wilkinson, 1997). One may speculate that, when estimating the risk/reward odds of initiating armed conflict, the limbic circuits of extant war planners may be firm-wired to perceive organized inter-group violence as it took place during the upper Paleolithic and Neolithic EEA (i.e., a raiding party for a low-risk attack against an unsuspecting settlement).

9.5. Fright-triggered bradycardic fainting as protection for the locus coeruleus (LC)

Clinical cardiologists consider fear-triggered vasovagal fainting "puzzling" since it is "hemodynamically paradoxical" (Benditt et al., 2004; Van Dijk, 2004). However, as we have argued elsewhere (Bracha et al., 2005a; Bracha, 2004) based on the last decade of work on PTSD's proximal-neurobiology, it may be helpful for neurocardiologists to re-conceptualize the simultaneous bradycardia and vasodilatation which are the defining features of fainting during real or perceived inescapable threat as akin to a protective "self-administered propranolol–prazosin combination" or (more physiologically accurately) "self-administered clonidine." From the neuroevolutionary psychiatry viewpoint, a rapid switch from tachycardic effroi (fright) to bradycardic faint may prevent progression from traumatic fear to PTSD by diminishing overconsolidational amygdala-driven hippocampal "searing" of fear traces. Several landmark studies (Vaiva et al., 2003, 2000; Pitman et al., 2002; Shalev, 2002) have demonstrated that prolonged episodes of fear-triggered ("peritraumatic") tachycardia and of peritraumatic effroi (fright) are both strong predictors of subsequent PTSD. Enhanced CNS noradrenergic post-synaptic responsiveness has been clearly shown to contribute to the pathophysiology of chronic PTSD (Southwick et al., 1993). This is consistent with the landmark study (Raskind et al., 2003) demonstrating the striking effectiveness of prazosin, a post-synaptic NE alpha-1 receptor antagonist, in the treatment of nightmares in veterans with CR-PTSD. The above is also consistent with the lower number of LC neurons we reported in a recent post-mortem study of three American WWII veterans with warzone-related PTSD compared to four control veterans (Bracha et al., 2005d). Arguably, prolonged combat-related LC overactivity may lead to what may be termed "overuse-driven LC neuronal loss." The overuse-driven LC neuronal loss may eventually result in upregulation of the denervated post-synaptic noradrenergic (NE) alpha-1 receptors, e.g., in the LC-to-basolateral-nucleus-of-the-amygdala (LC-BLNA) pathway. Arguably, the evolved trait of fright-triggered efferent vasovagal faints during overwhelming inescapable stress (discussed above) may have been evolutionarily conserved as a protective fitness-enhancing trait (shutting down LC firing/sparing the LC/diminishing NE-driven overconsolidation/preventing upregulation of the denervated post-synaptic NE alpha-1 receptors and thus preventing the enhanced noradrenergic post-synaptic responsiveness in the LC-BLNA pathways and related LC efferents).

9.6. Contributions of neuroevolutionary psychiatry to the forthcoming refinement of the Department of Veterans Affairs (VA) PTSD Compensation and Pension (C&P)

As noted earlier in the section discussing Cenozoic (simian-wide) fear-circuits, two physical objective signs of anxiety, fear-induced bite-muscle-strengthening (acute jaw clenching, gnashing) and incisor-sharpening (chronic teeth grinding, bruxing), can be widely observed in fear circuitry disorder clinics, such as VA PTSD clinics (Bracha et al., 2004d,e, 2005f). We have argued elsewhere that clinicians may want to consider adding to the anxiety-disorder-specific examination (such as the VA PTSD C&P exam) the palpation of the masticatory muscles (masseter and temporalis) and the inspection of the front incisors for these two physical signs of fear circuitry activation to provide corroborating physical evidence in support of the veteran's self-report of severe ongoing anxiety symptoms (Bracha et al., 2005e).

9.7. PTSD Criterion-D and PTSD Criterion-A2 in the forthcoming DSM-V: towards revisions based on evolutionary reasoning

Additionally, one of the PTSD diagnostic criteria that is very likely to undergo a substantial revision in DSM-V is PTSD Criterion-D (persistent fear circuitry activation not present before the trauma). Research is needed to examine the possible incremental positive predictive value of incorporating various physical signs into DSM-V PTSD diagnostic criteria (Bracha et al., 2005e,f, 2003; Bracha, 2004). Grinding-induced incisor wear and clenching-induced palpable masseter tenderness may be examples of such physical signs of persistent fear circuitry activation not present before the trauma (PTSD Criterion-D) (Bracha et al., 2005e). Elsewhere we have made similar arguments regarding the need to revise PTSD Criterion-A (Bracha et al., 2004a,c; Bracha and Bienvenu, 2005).

9.8. Predictions regarding PTSD following large-scale bioevent disasters such as zoonotic pandemics

It may not be immediately obvious, but neuroevolutionary principles may also need to be considered during the preparation for bioevents such as zoonoses-triggered pandemics e.g. avian influenza pandemics and Severe Acute Respiratory Syndrome (SARS). Strong affection for domesticated fowl and domesticated pigs evolved in humans for over 12,000 years. In contrast, the agricultural practices likely to create conditions favorable to re-assortment-triggered genomic shift, and to pandemics in general, only appeared with the emergence of cities and societies with very high population density, mostly in the last 4000 years. Thus it is posited that epizoonoses and zoonotic pandemics can be conceptualized as human-caused (rather than natural) disasters. The author predicts that both intentionally-caused large-scale bioevent-disasters, as well as natural bioevents such as SARS and avian flu pandemics, will be an exception and are likely to be followed by PTSD rates approaching those that follow warzone exposure. During bioevents, *amygdala-locus coeruleus-driven epidemic pseudosomatic symptoms* may be an order of magnitude more common than infection-caused cytokine-driven symptoms. For the above two reasons, it is critical that during pandemics and especially intentionally-caused bio-events, rapid telephone screening be conducted for acute limbic-triggered pseudosomatic symptoms as well as for predictors of PTSD (Criterion-A2, tachycardia, etc.) (Bracha & Bienvenu, 2005; Bracha & Burkle, unpublished).

10. Red Cross and FEMA Implications. "Seeking Safety in Numbers" is a non-survival-enhancing hardwired fear-based decision likely to occur during bioevent disasters

Neurally modern humans are hardwired to seek the company of other humans when experiencing hypervigilant fear. As we argued elsewhere (e.g., Bracha, 2004), unless immediately managed, hypervigilant fear is rapidly followed by an urge to flee (as part of the hardwired hypervigilance, flight, fright, faint, acute stress sequence). The "flight response" is hardwired and thus makes common sense both to bioevent victims and to federal emergency management leaders. Consequently, current emergency management practices, including those of the Red Cross and the Federal Emergency Management Agency (FEMA), are almost set in stone and designed to help disaster victims flee to centralized shelters, rather than shelter themselves in-place (at home). A forceful national effort is warranted to change these engrained disaster-response practices.

11. Conserved foraging circuits and subsequent preverbal trauma in extant toddlers

What is termed here "foraging-circuit-driven traits" is a construct akin to novelty-seeking traits and the construct of hypophobia discussed earlier. During human toddlerhood (although surprisingly little research is available), being electrocuted is arguably the most severe Criterion-A experience possible. Two major risk factors for chronic PTSD, severe pain (Jehel et al., 2003) and extreme fright (Vaiva et al., 2000, 2003) are simultaneously inflicted on a toddler when he or she is electrecuted. A question relevant to the evolutionary context at hand is why preverbal toddlers insert thin metal objects (e.g., screwdrivers, nails or knitting needles) into electric sockets in the first place. The mode of acquisition of inserting thin straight metal objects into electric sockets is presently unclear. These objects do not share stimulus properties with electric cords, thus observer conditioning is unlikely. However, ample chimpanzee-socioecology research on *P. troglodytes* feeding habits has found that chimpanzees engaged in "termite fishing" by inserting thin straight branches into entry points in termite mounds. Interestingly, this behavior can arguably be better defined as "foraging for termites" since it is mostly observed in female chimpanzees and sub-adult chimpanzees including sub-adult males who are still unable to participate in the hunt for small mammals (e.g., Colobus monkeys which are the main prey of adult male *P. troglodytes*). The mode of acquisition of

termite foraging behavior is intensely debated, and arguably, is at the very least, prepotentiated. Insertion of metal objects into electric sockets by a still-undermyelinated human brain may be a result of activation of the evolved firm-wired termite-foraging circuits. There is a wide consensus among paleoanthropologists that, along with larvae, termites were a source of fat and high quality protein for early hominins (Brothwell and Brothwell, 1998). The termite-hunting-circuit hypothesis of preverbal-electrocution trauma is safely testable in human toddlers.

12. Iatrogenic overconsolidational disorders which may need a re-taxonomization in DSM-V (hospital phobia and dental phobia)

12.1. Posttraumatic medical-care anxiety (hospital phobia)

In their landmark Baltimore ECA follow-up study, Bienvenu and Eaton (1998) reported that patients with fear of blood, injection, or injury do not have comorbid fears of medical clinics, physicians, or hospitals. Bienvenu and Eaton's (1998) findings are consistent with the prediction that "hospital phobia" is a PTSD-like overconsolidational fear. Arguably, the heritability of blood-injection-injury phobia (narrowly defined as fear of blood, injection or injury) may be underestimated by the misclassification of hospital avoidance, which is posited here to be mostly overconsolidational. It is difficult to envision an EEA Criterion-A adversity that remotely resembles a hospital stay. However, more research regarding the mode of acquisition of hospital avoidance is needed.

12.2. Posttraumatic Dental-care Anxiety (PTDA)

More research is also needed on "dental phobia" since the available data are inconclusive (Poulton et al., 1997). Dental phobia most probably a heterogeneous category consisting of 1) an innate fear of sharp objects in close proximity to one's head and neck, 2) innate fear of drowning (choking on saliva) and 3) probably most commonly, a non-innate overconsolidational fear following a very painful dental procedure (Bracha, Vega and Vega, submitted for publication). Important recent research by Jehel et al. (2003) on survivors of a bomb attack in a Paris subway in December 1996 is relevant in this regard. As Jehel et al. (2003) have demonstrated, physical pain/injury during the Criterion-A adversity is a previously neglected risk factor for subsequent overconsolidational disorders such as PTSD. Bracha, Vega and Vega (submitted for publication) have argued that problem with using the term "phobia" in a dental-care context is as follows: by definition, phobias involve a fear that is "excessive or unreasonable," which the individual recognizes as such, and in which the anxiety, panic attacks and phobic avoidance are not better accounted for by another disorder, including PTSD. More research is needed, however most individuals with dental "phobia" do not recognize their symptoms as "excessive or unreasonable" and, in that sense, resemble individuals with PTSD. Our review of the dental-care literature suggests that true (innate) dental phobias (akin to unreasonable fear at the sight of blood or a syringe) probably account for a smaller percentage of cases, and that the vast majority of dental-care anxiety (DA) cases stem from aversive dental experiences. Research has documented that individuals who reported having experienced *painful* dental treatments and perceived a lack of control in the dental situation were approximately 14 times more likely to also report higher dental fear, and approximately 16 times more likely to report being less willing to return to the dental treatment. Therefore, this psychological condition may be better conceptualized as Posttraumatic Dental-care Anxiety (PTDA), and should be classified as part of the overconsolidational disorders spectrum in the forthcoming DSM-V.

13. Overconsolidational fear of animal attack: dog, bird, or bat phobia (may also need to be re-taxonomized in DSM-V)

13.1. Overconsolidational fear of dogs

In light of the symbiotic 15,000-year-long co-evolution of humans and dogs, and humans' long dependence on dogs for both hunting and protection, neuroevolutionary reasoning predicts that fear of dogs has an associative mode of acquisition. The anecdotally reported improved sleep achieved by a prescription of having a large dog share the patient's bed also suggests that the "anxiolytic effect of dogs" is innate and that, thus, fear of dogs develops overconsolidationally. There is almost no published research on this fear. However, in a study of 30 children with dog phobia, over 86% of parents "were able to attribute their child's phobia to one of Rachman's three (non-innate) conditioning pathways: direct conditioning, modeling, or transmission of information" (King et al., 1997). Clinical data reviewed by Marks (1987) are also consistent with an overconsolidational mode of acquisition of the fear of dogs. In most studies unfortunately, fear of dogs is grouped in the "other" animal sub-category, (Kendler et al., 2002) so it is not possible to draw conclusions from their data at this stage.

13.2. Overconsolidational fear of birds

Similarly, neuroevolutionary reasoning predicts that fear of avians is also not an innate fear. Paleoanthropological studies document that, even before the development of archery technology, avians were a common human prey (presumably caught with nets) (Brothwell and Brothwell, 1998). In the Kendler et al. twin study (Kendler et al., 2002), fear of birds is also grouped in the "other" animal sub-category, so it is not possible to draw conclusions from their data at this stage.

13.3. Overconsolidational fear of bats

Neuroevolutionary reasoning predicts that (like fear of domesticated canids and of avians) fear of bats is over-consolidational. There is currently widespread consumption of bats, in Africa, Asia, and the Pacific Islands, especially in the Commonwealth of the Northern Mariana Islands (e.g. Saipan, Tinian, and Rota), as well as among Chamorro Americans in

Guam. Research has found that bats and the *H. sapiens* have shared caves at least since the beginning of the lower Paleolithic (i.e., ~2 million years). The Kendler et al. (2002) twin study is consistent with an associative mode of acquisition proposed herein for bat phobia. Out of 37 subjects with fear of bats, 62.2% reported "trauma to self" from bats, and only 5.4% had "no memory" (a 12:1 ratio). In contrast, as noted above, among "bug phobia" subjects, 40.6% reported "trauma to self" and a very high 43.8% reported "no memory" (a one to one ratio) (Kendler et al., 2002). These findings are consistent with the neuroevolutionary prediction that fear of bats is overconsolidational. More research is needed.

13.4. Falsifiable predictions that follow from the above reasoning on dog, bird and bat phobias

The first falsifiable prediction that follows from the above reasoning is that the heritability of dog, bird and bat fears may be quite low and closer to that of PTSD, the prototypical overconsolidational disorder. The second prediction is that Pitman's propranolol anti-overconsolidation regimen (Pitman et al., 2002; Pitman and Delahantly, 2005; Vaiva et al., 2003) will be an effective and useful addition to the standard emergency management protocol for individuals presenting with these three animal injuries. The second falsifiable prediction is based on the finding of Jehel et al. (2003) (discussed above). It is predicted that painful injury will be a key risk factor for subsequent dog, bird or bat phobia. Anecdotally, facial injury from a flock of bats or birds is often seen in rural emergency departments. If dog phobia, bird phobia and bat phobia are non-innate as posited here, these fears can be clustered in a new "overconsolidational disorders" category in the DSM-V discussed above with regard to PTSD.

14. Towards a science-based DSM-V reconceptualization of anxiety disorders which DSM-IV-TR currently labels 'culture-bound'

Among stress-neurobiology researchers working with Asian Americans and researchers in East Asia, there is a growing consensus that the research agenda for the DSM-V should include a major re-conceptualization of what the DSM-IV-TR terms "culture-bound syndromes." An attempt should be made to place these syndromes in a more neurobiological context in the forthcoming DSM-V. A clinical imperative for such a re-conceptualization is that a failure by primary care clinicians to assume a standard DSM diagnosis of these patients results in a failure to make a referral to psychiatric science-based interventions. Such patients are left to seek non-science-based and often harmful "alternative medicine." A re-conceptualization is also important because cross-cultural and ethnocultural research suffers from the use of unhelpful terms such as "race" rather than "geographic ancestry" (Bamshad, 2005). Geographic ancestry (as self-reported) can easily tackle methodological problems resulting, for example, from the lumping (in research settings) of individuals of Puerto Rican, Cuban, Mexican, south American, Central American and European–Spanish ancestry as "Hispanic." Another example of a problematic social construct is "Asian Americans and Pacific Islanders" used widely in cross-cultural and ethnocultural research. The construct of "Asian Americans and Pacific Islanders" clusters Pacific Islanders (e.g., Samoans) with Americans of North Asian geographical ancestry (Japanese/Koreans). This clustering is scientifically incorrect. As Bamshad (2005) has recently argued, at least in the U.S. and in other countries with high admixture, "geographic ancestry" (e.g., self-reported using three-generation checklists or triangular graphs) needs to replace self-reported "race," since geographic ancestry is a much better proxy of relevant allele frequencies and probably also of a person's culture.

15. Taijin-kyofusho

One of the symptom clusters that DSM-IV-TR erroneously contends is unique to the Japanese culture-bound genome is taijin-kyofusho. In the U.S., it is primarily diagnosed in Hawaii, but there are no research data suggesting that taijin-kyofusho is a useful construct. Suzuki et al. from Japan have recently criticized the conceptualization of taijin-kyofusho in DSM-IV-TR (Suzuki et al., 2003). Suzuki et al. (2003) state that there was "an erroneous introduction of taijin-kyofusho to the West." Furthermore, these authors state, "the three subtypes of taijin kyofusho are not culturally distinctive phobias in Japan" and that "at this stage, the notion that taijin kyofusho is a culture-bound syndrome cannot be held." Suzuki et al.'s conclusions are consistent with our suggestion that taijin-kyofusho is one of a dozen or so DSM-IV-TR terms that should not be carried over in DSM-V. Instead, taijin-kyofusho may be more coherently conceptualized as comorbidity of any two of the following evolutionarily driven anxiety traits which may be equally prevalent in the West and in Japan. These are three mostly innate and well understood disorders for which science-based treatments are available: Generalized Social Phobia, Body Dysmorphic Disorder, and an obsessive preoccupation with one's personal cleanliness and body odor as part of OCD.

16. "Koro," "shuk yang," "shook yong," "suo yang," "rok-joo," and "jinjinia bemar"

These disorders are also listed in DSM-IV-TR (APA, 2000) as culture-bound (p. 900). In the U.S., the disorders are probably most often seen in Hawaii, Guam and American Samoa. All consist of an intense acute fear that the external genitalia (in males) or nipples (in females) will retract into the body and potentially cause death. The author posits that these six syndromes are essentially identical to either panic attacks or other well-understood acute anxiety states in which the evolutionarily hardwired sympathetic (Fives F's) evolved acute fear response includes a fitness-enhancing and protective retraction of the external genitalia as part of the freeze–flight–fight–fright response. In women, the manifestations include a retraction of the nipples and blanching of the areola, which may be understood as fear-induced cutaneous vasoconstriction. Arguably, the reason why these signs of acute anxiety are usually reported from peri-equatorial countries may simply be that

minimal clothing makes them more easily observable. Maintaining the description of these syndromes as "culture-bound" may prevent science-based treatment and may be stigmatizing.

17. "Karoshi", "gwarosa" and "Voodoo death" (a fear-induced malignant syncope?)

Arguably, "karoshi", "gwarosa" and "Voodoo death" are not useful constructs but rather are identical to fear-induced malignant syncope (FIMS) observed in Europe and the US. The traditional Japanese diagnosis of karoshi is a medically unexplained sudden cardiac death in a young otherwise healthy male after a public humiliation by a powerful authority figure (karoshi is often translated as "job stress death"). Voodoo death is another medically unexplained fear-triggered cardiac death usually reported in young, otherwise healthy males. It is still widely observed in countries with extremely high levels of lethal violence such as Haiti. The author posits that both karoshi and Voodoo death may be identical to FIMS. FIMS (efferent vasovagal syncope of malignant severity) is the most common indication for insertion of a pacemaker in young adults in the US. Malignant (lethal) vasovagal syncope has been perplexing to cardiologists who consider its etiology "puzzling" and a "riddle" (Benditt et al., 2004; Van Dijk, 2004), but as we have argued in two recent articles (Bracha et al., 2005a; Bracha, 2004), reflex vasovagal syncope of malignant severity may simply represent the extreme pathological tail of heart rate variability described above as a key component of fear-induced fainting. FIMS is arguably the best physiological explanation not only for karoshi and for Voodoo death, but also for the historical and ethnographic reports of healthy individuals being "stricken dead" by a verbal threat.

18. Agoraphobia with and agoraphobia without a history of panic attacks: two different modes of acquisition?

The widely held view of agoraphobia is that it is invariably a post-panic-attack fear overconsolidation. If so, "phobia" is an inappropriate suffix that warrants reconsideration in DSM-V. Horwath and Weissman (2000) have argued that the National Comorbidity Study (NCS) data and the reanalysis of ECA data are both consistent with Klein's conditioned-avoidance hypothesis of agoraphobia (Klein, 1981). In its updated version (Kent et al., 2005; Gorman, 2004), this hypothesis posits an overconsolidation-based avoidance mostly secondary to previous spontaneous orbitofronto-amygdala-circuit-driven panic attacks (Kent et al., 2005). It is noteworthy that agoraphobia and social phobia are the only two phobias in which Kendler et al. (2001) found that family environment may have an impact on risk. Nevertheless, moderate heritability of agoraphobia was demonstrated in the same study (Kendler et al., 2001). The small subgroup of agoraphobia that has no history of panic attacks has been more difficult to explain (even when taking into account the likelihood of poor self-report). In the context of this article, the existence of a primary agoraphobia (with no panic attacks) is predicted by evolutionary reasoning. It is tempting to speculate that primary agoraphobia may be traced back to the fact that humans (medium sized and relatively slow mammals) were partially arboreal until about 3 Mya. Thus, early hominins arguably relied on arboreality as their primary escape response (the flight segment of their freeze, flight, fight, fright sequence). Numerous theorists (e.g., Tooby and Cosmides, 1990a; Morgan et al., 2004) have argued that expanding beyond the forested highland indigenous niche and moving into almost treeless wide-open savannahs increased the vulnerability of humans to predation by faster-moving carnivores, primarily large felines, and thus made fear of wide-open (treeless?) spaces a fitness-enhancing trait. A falsifiable prediction is that patients with primary agoraphobia would be less anxious in a virtual reality landscape which is not entirely treeless. Arguably, the anxiolytic effect of nearby tall trees (and affection for tree houses among prepubertal extant *H. sapiens*) may be a manifestation of these still partly conserved circuits, and may thus be over-represented among first-degree relatives of primary agoraphobia probands (this prediction is testable).

19. Brief comments regarding often-cited 1970s critiques of neuroevolutionary reasoning

The severity of anxiety symptoms addressed by neuroevolutionary psychiatry is harder to explain as stochastics or spandrels. "Neuroevolutionary psychiatry" (as this term is defined in this article) attempts to offer clinically useful predictions relevant to the research agenda for the DSM-V and be useful to psychiatric genetics. It is axiomatic that "the human ability to unlearn things one has never learned" (that are innate) is commonly observed. Thus, the common social science critique that innate fears, e.g., of snakes, can often be successfully extinguished by exposure does not contradict their evolutionary-based etiology. As discussed in Introduction, evolutionary psychology focuses on universal human traits which are species-typical in humans and thus have low heritability (Tooby and Cosmides, 2005; Cosmides and Tooby, 1999, 1992). Nevertheless, a brief discussion of and defense of the sister specialty (evolutionary psychology) may be warranted. The critique that evolutionary psychology is just a collection of untestable Lamarckian Rudyard-Kiplingian "just so stories" was raised in a widely cited theoretical paper written a quarter-century ago by two highly influential non-paleoanthropologists, Gould and Lewontin (1979). Interestingly, the "just so stories" critique was also made about Darwin's work. While neuroevolutionary hypotheses of stress and fear circuitry disorders are still speculative, they are empirically falsifiable in numerous ways as proposed in this article. It should be noted that Gould and Lewontin (1979) write with a dualistic Cartesian mind–body dichotomy probably because their expertise is in insect and dinosaur evolution where gene–culture co-evolution does not occur. For complete lucid rebuttals of Gould and Lewontin's "just so stories" critique, see reviews by Wakefield (1992), Buss et al. (1998) and Tooby and Cosmides (1990b) and recent syntheses of the newer research by Dawkins (2004). Finally, a statistical language to express causation has yet to emerge (Pearl, 2000), and research into etiological factors in psychiatric disorders traditionally begun as a "just so story." The author is in full agreement with Gould and Lewontin (1979)

that, at present, an unknown percentage of differences which appear on the surface to be evolved behavioral traits (including some of the hypotheses presented in this article) will be found to be evolutionary design compromises or reflect random genetic drift. However, hidden among the brain expressed genomic differences are at least a significant percentage of functionally relevent DNA (most likely in Introns) that underlie the brain-expressed phenotypic differences between clinically symptomatic and non-clinically symptomatic humans. Gould and Lewontin's other claim that "behaviors do not leave fossils" may also be challenged by a wide range of emerging techniques, such as the study of fear-circuitry-related infradian fluctuations (e.g., of NE Beta-receptor activity, or vagal nucleus ambiguus firing) as reflected in human mineralized tissue (Bracha et al., 2004b; Takeda et al., 2002; Larsen, 1999). More importantly, the "behaviors do not leave fossils" claim also is not supported by molecular-phylogenetic studies of human lineages via chromosome-Y and mitochondrial DNA (Underhill et al., 2001; Seielstad et al., 1998). Finally, if we fully adhere to Gould and Lewontin's forensic criteria of level of evidence, Darwin's 19th century theory of common ancestry for the *Homo* and *Pan* lineages was a "just so story," only proven as fact on September 1, 2005 with the publication of the paper *Initial Sequence of the Chimpanzee Genome and Comparison with the Human Genome* completed by the Chimpanzee Sequencing and Analysis Consortium (CSAC, 2005).

20. Gene–environment interactions ("ontogenomics") and caveats

20.1. The non-reductionistic evolutionary perspective

It is important to emphasize that this article espouses a non-reductionistic evolutionary perspective which is not only consistent with a key role for pleiotropic genes, and other design compromises but also does not discount the important role of epigenetic factors, psychological and physical ontogenomic (early environment) factors, the heterogeneity and multifactoriality of anxiety traits, allostatic load, social support group cohesion and horizontally transmitted (culturally learned) factors such as religiousness (Bracha and Hayashi, in press) and lifestyle choices. This non-reductionistic clinically oriented approach emphasizes the importance of clinically treating those behavioral traits that evolved for Cenozoic, Paleolithic, or Neolithic environments, and which have outlived their usefulness in extant human adults. While evolutionary factors of anxiety traits are the sole focus of this article, the "frontal release phenomena" heuristic of clinical neuropsychiatry deserves mention since it may be helpful for a constructive fusion of distal (evolutionary) neurobiology with "clinical proximal neurobiology." Kent et al. (2005) emphasize the importance of "appropriate top–down governance by frontal cortical regions over a hypersensitive amygdala-centered fear neurocircuitry." The frontal release phenomena heuristic may help explain why some archaic fears are inversely correlated with age, between childhood and early adulthood, as the top–down governance of the frontal cortex over the amygdala increases. Additionally, the frontal release-sign heuristic may similarly explain why there is a positive correlation between late-life frontal lobe dysfunction (e.g., Alzheimer's disease) and the resurfacing of fears that evolved for earlier segments of the human EEA, and which may have outlived their usefulness in extant *H. sapien* adults.

21. Objections to evolutionary reconceptualizations for DSM-V are to be expected

Some initial ideology driven objections to any mention of evolutionary etiological factors in DSM-V are to be expected. First and foremost, for the severest psychiatric illnesses, neuroevolutionary perspectives are clinically unhelpful (schizophrenia is the best example). In contrast, it is axiomatic that a mild degree of fear is helpful and that one can have "too much of a good thing" (too high a gene dosage?). Therefore, a prudent strategy in the research agenda for DSM-V may be to focus initially on evolutionary factors in fear circuitry disorders. A second objection may stem from the sometimes overlapping language between neuroevolutionary psychiatry and psychoanalytic theory which understandably makes psychiatric researchers uneasy. However, there are obvious fundamental differences between psychoanalytic theory and neuroevolutionary psychiatry. For example, psychoanalysis focused on ontogeny while neuroevolutionary psychiatry presents hominin-phylogenetic-based hypotheses and eventually may be able to focus on phylogenomics–ontogenomics interactions (a.k.a. gene–environment interactions) at the molecular level. To some degree, hominin phylogenomics can be seen as the basic science of evolutionary psychiatry. As Table 2 (above) attempts to demonstrate, phylogenomics may fit well into the spectrum of investigational methods into the etiology of fear circuitry disorders.

22. Conclusion

It is important to emphasize that hypotheses are by definition conjectural. At this stage, the data in support of re-clustering fear traits neuroevolutionarily or phylogenomically are still very limited and the hypotheses presented in this article are highly speculative. Epidemiological and twin studies are needed to test whether clustering fear-related traits by neuroevolutionary time-depth may be one of the useful non-phenotype-based approaches to anxiety disorders in the research agenda for the forthcoming DSM-V. As noted earlier, discussion of etiological factors in DSM-III (APA, 1980), DSM-IV (APA, 1994), DSM-IV-TR (APA, 2000) and ICD-10 (WHO, 1992) has been judiciously minimized. In contrast, the research agenda for the forthcoming DSM-V has specifically highlighted the need for a more etiologically based classification (Kupfer et al., 2002; Charney et al., 2002). Furthermore, as several authorities have noted (Kupfer et al., 2002), examination of the usefulness of adding an Axis VI reflecting evolutionary factors can be a part of the research agenda for the forthcoming DSM-V. Early theorists such as Bowlby (1975) and MacLean (1985) unfortunately focused on human-species-typical (and thus

non-clinical), "basic" fear circuits which are phenotypically expressed almost exclusively in undermyelinated humans (infants and toddlers). These are the circuits that MacLean labeled "paleo-mammalian," and which in this article are termed Mesozoic. In contrast, the neuroevolutionary synthesis and re-clustering of fear-circuitry-related traits proposed here attempt to go beyond Bowlby's (1975) and MacLean's (1985) writings by focusing exclusively on fear circuits which are species-specific in humans (and much more importantly *human-species-atypical*, and thus clinically relevant) as well as phenotypically expressed in adult clinical populations. Over 30 empirically falsifiable predictions relevant to the DSM-V research agenda on fear circuitry disorders are presented. In addition to discussing fears which are primarily innate, the author presents a dozen evolution-based testable predictions relevant to research on overconsolidational fears, especially warzone-related PTSD. Finally, to the best of the author's knowledge, the Neuroevolutionary Time-depth Principle (Neuroevolutionary-TDP) introduced in this review is the first to tackle the question of why extant humans are consistently found to have a much higher resilience following exposure to natural disasters than following personal engagement in lethal fighting (combat), being personally present when conspecifics engage in lethal fighting (warzone exposure) or being personally present during intentionally caused disasters such as terrorism.

Acknowledgements

This material is based upon work supported in part by the Office of Research and Development, Medical Research Service, Department of Veterans Affairs, VA Pacific Islands Health Care System, Spark M. Matsunaga Medical Center. Support was also provided by a National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award, and the VA National Center for PTSD. The author thanks Stacy Lenze, Michelle Tsang Mui Chung, Jessica Shelton, and Nicole Masukawa for outstanding editorial assistance. Views expressed in this article are those of the author and may not reflect views of the author's employer or related institutions. All potential clinical applications of currently marketed drugs in the United States discussed in this article are "off-label."

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