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Theoretical Paper

An approach to the prevention of anxiety-related disorders based on evolutionary medicine

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Abstract

Anxiety-related disorders are among the more common ailments of modern societies. Presumably, their prevalence is partly due to environmental factors, which suggests that anxiety may be one of the health problems that are aggravated by discords (adverse mismatches) between the present way of life and what our genes are adapted to. Consequently, it may be possible to find preventive measures by using the perspective of evolutionary medicine. I shall argue that the prevalence of anxiety-related problems reflects that the nerve circuitry and endocrine activity associated with the fear function have developed beyond normal. Moreover, that this expansion is due to excessive or abnormal triggering, particularly at an early age. Possible discords that may be responsible, such as present child care practices, will be discussed.
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Introduction

Fear is an innate mammalian function with an obvious adaptive value [1–3]. Compared to other complex functions involving the brain, fear has a reasonably well-understood neurology, endocrinology, and genetics [4–7]. Fear is an effective stimulator of the 'fight-or-flight' response, also referred to as the acute stress response, which implies activation of the hypothalamic–pituitary–adrenal (HPA) axis. The rational for this response is presumably to prompt the animal to either flee (if escape is likely) or freeze/hide (if escape is not an option).

The term anxiety may be considered synonymous with fear, but is typically used for the debilitating state caused by inappropriate or excessive triggering of the fear function, such as in phobias and generalized anxiety disorder. Long-term excessive or inappropriate triggering of the fear function may be defined as anxiety disorders according to diagnostic manuals (ICD/WHO or DSM/APA). In addition to reducing the quality of life of the sufferer [8], the condition may lead to various secondary ailments, such as stress-related diseases [9,10] and depression [11]. Moreover,

in both animals and humans, a high level of anxiety correlates with a shortened life span [9,12,13].

According to the National Institute of Mental Health, some 10% of adult Americans suffer from anxiety disorders [14]. Considering the secondary consequences of excessive anxiety and stress, and that even milder versions of anxiety, not considered pathological, may reduce quality of life [8], anxiety appears to be among the more taxing health problems in modern societies [15].

The evolutionary perspective has proven valuable in suggesting causative factors where the prevalence of a disease or a condition is in excess of what one might reasonably expect would be the case for humans living in an environment to which they were genetically adapted [16–19]. The high proportion of people suffering from debilitating problems related to anxiety indicates that this is such a condition; in a natural setting, one would not expect such a function to become incapacitating except in extreme cases. I shall combine current understanding of the fear function with the evolutionary perspective in order to propose possible causes for the prevalence of anxiety-related problems, and thereby point towards preventive measures.

A central assumption of evolutionary medicine is that, as a rule of thumb, both animals and humans are designed to thrive under the conditions to which their genes are adapted.

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These conditions, sometimes referred to as the *environment of evolutionary adaptation* are, in the case of humans, presumably akin to the typical way of life of the late Pleistocene, prior to the invention of agriculture [18]. Disparities between this way of life and that of present societies are referred to as *mismatches*. However, not all mismatches are unfavorable, for example, sleeping on a mattress may be as healthy as sleeping on the ground. The mismatches that are potentially detrimental may be referred to as *discords* [20].

Fear in an evolutionary perspective

There are differences as to what sort of signals animals are predisposed to respond with fear, and as to how fear is learned, but the underlying neurology and endocrinology of the response appear to be remarkably similar across mammalian species [4,6]. Thus, animal models are presumably useful for understanding the physiology of fear. Moreover, some of the health consequences of excessive anxiety and stress also emerge in mammals.

The importance of reacting with fear in a situation that may imply danger has caused evolution to design this response to be easily triggered. Due to the much greater fitness cost of not responding to a real danger, compared to superfluous response to a non-existent danger, we are apparently tuned to react rather too often than too late [16].

Fear stimuli activate both conscious and non-conscious functions. The non-conscious includes the HPA axis, as well as nerve circuitry-sending stimuli toward this axis. The conscious part allows us to cognitively modulate the fear response. It is of obvious adaptive value to be able to learn up to what extent various stimuli ought to be considered dangerous. This learning process does not require conscious functions, but in humans, cognitive evaluation can influence the process. The success of cognitive therapy rests on this capacity to overcome phobias and other fears. However, fear may also be learned, for example, by conditioning or by social transmission. Thus, the consequence of experiencing repeated traumatic or fearful situations may be that the response is either subdued or augmented. It follows that a person exposed to a particular type of distressing stimuli early in life may turn out to be either less or more prone to develop related phobias [16,21].

The human body was not designed with the pleasure of its occupant in mind. A main function of fear is, as in the case of pain, to teach us to avoid dangerous situations. In order to fulfill that purpose, fear has qualities that cause most people to consider it unpleasant, at least in situations that are not deliberately sought and thus under voluntary control. Moreover, once triggered, both fear and pain will tend to dominate the conscious mind. Yet, the absence of fear may lead to injury or death, and should therefore not be coveted; just as the lack of pain is a potentially lethal disease [1,16,21].

Individuals differ, due to both genetic and environmental variables, as to how easily fear is elicited and anxiety disorders develop [2,22]. Recently, some of the genes contributing to individual differences have been discovered [23,24]. Even in the Paleolithic, some individuals were probably more anxious than what might be considered necessary or optimal. However, based on the prevalence of anxiety-related problems [14,25,26], it seems likely that the distribution of anxiety since then has shifted towards higher levels. That is, one would not expect the fear function to be designed by evolution in such a way that a substantial fraction of the population suffers from obviously irrational, maladaptive, and more or less debilitating anxiety.

The concomitant distress and malady is unfortunate, considering that one may argue that the preferred level of fear function activity is lower for contemporary inhabitants than for Paleolithic people: for one, we have better cognitive knowledge of potential dangers; and two, some of the dangers we are designed to respond to with particular vigor barely exist today (such as snakes and predators), while the fear function may not offer optimal protection against more realistic dangers (such as smoking, narcotics, and traffic).

The hyperactive fear function

It is generally recognized that most bodily and mental function will tend to increase in power and performance upon stimulation and use. The fear function appears to be no exception. The expansion of the endocrine glands involved in stress has been known for a long time [27]. People prone to respond with fear tend to develop a more pronounced HPA response than do less fearful individuals [4,6]. Moreover, it is well known that brain functions tend to develop upon use, by both physical expansion and improved efficacy, as nicely illustrated by the centers allocated to interpreting signals from rat whiskers [28]. In other words, current knowledge suggests that the non-conscious, biochemical, and anatomical substrates underlying anxiety expand upon exposure to anxiety-inducing stimuli. The problem is that whereas we, in most cases, appreciate the fact that mental and physical functions can improve upon practice, when it comes to anxiety, it can work to our disadvantage.

A variety of mental problems are recognized as consequences of inappropriate activity of the fear function: besides the generalized anxiety disorder, people suffer from various phobias, panic disorders, and post-traumatic stress disorder [1,4]. Presumably, all these conditions are associated with excess activity of nerve circuitry and endocrine glands related to fear. The diversity of problems reflects that there is not one particular structure of the brain that deals with all aspects of anxiety and fear, but rather a complex mixture of interacting circuitry, which tend to converge, if not elsewhere, on the HPA [1,4,6]. Panic attacks, for example, appear to primarily involve a center associated

with separation distress in infants, which again seems to be evolutionary related to circuitry associated with pain [4]. However, the principle of expansion due to excessive stimuli may very well be applicable to all underlying structures, and the term 'fear function' is here meant to cover them all. Moreover, the different systems most likely interact and use shared brain and endocrine functions (for example the HPA-axis); thus, unwarranted expansion of one part, such as general anxiety, may cause the individual to be more vulnerable to other forms of anxiety as well, such as phobias or panic attacks. The point is reflected in the high co-morbidity of various anxiety-related problems [2,29].

Apparently, the cognitive assessment of dangers is not off in people with anxiety disorders, instead they overreact to cues, or react even in the absence of cues, due to the hypersensitivity of the system [30]. This observation supports the notion that the problem typically rests with unwarranted sensitivity of the non-conscious part of the fear function.

Certain forms of anxiety disorders, such as generalized anxiety, may develop slowly and thus be more pronounced in adults [31]. Yet, anxiety is the most common psychiatric condition in children, an estimated 9% have at least one anxiety-related problem [25,26]. Cases of late onset may reflect that the problem develops over time, as continuous stimulation gradually cause key components to expand and dominate. One would expect a shift upon aging from phobias (excessive fear in situation where it is natural to show some fear), toward more generalized anxiety. For one, because adults may acquire cognitive control of specific fears, and two, because the underlying non-conscious structures may continue to expand and therefore gradually become less responsive to cognitive inhibition. It is relevant to note that even when a particular fear eventually is subdued, the previous stimulation of the fear function may have contributed to the expansion of the underlying non-conscious components of this function.

It is well known that the early months and years of life are critical for brain development, and one would therefore expect that discords early in life tend to have a worse impact than adult discords [19]. Recent research on rodents support the contention that excess anxiety in infants may have dire consequences [7,32]. It is well known that increased activity of the neurotransmitter serotonin tends to reduce anxiety (reflected in the fact that serotonin reuptake inhibitors are commonly used to treat anxiety disorders), and that the serotonin 1 A receptor is of particular importance in both animals and humans [24]. One way of decreasing the activity of serotonin in experimental animals is to constitutively or conditionally inactivate the gene for this receptor. Using these methods, it has been shown that the expression of the serotonin 1 A receptor in the hippocampus and cortex is required to avoid excessive anxiety in young mice. Moreover, the presence of this receptor during a critical period of postnatal development is required to avoid unnecessary anxiety in adults. Turning the receptor on again

in adults does not improve the situation, and turning it off solely in adults has little effect.

Thus, although adult anxiety disorders may reflect both the expansion of the fear function during infancy, and the stress of adult life, it makes sense to be particularly concerned about the environment of children. This is because discords during the early period of brain development may lay the foundations for later problems; but also because it may prove more difficult for adults to avoid stress, compared to giving infants an environment that does not cause unnecessary anxiety.

Discords that may explain excessive fear function activity

Although we know that some genotypes are more vulnerable than others [23,24], genetic epidemiology suggests that anxiety-related problems are also due to environmental conditions, including social interactions [2,33]. Particular traumatic experiences have been assumed to be the environmental factor causing phobias, for example, nearly drowning at a young age might cause adult water phobia. However, recent research suggests that other environmental factors may be equally important [21,34]. In fact, the main environmental impact may be more in the direction of a general increase in the susceptibility to anxiety-related problems.

It follows from the prevalence of pathogenic forms of anxiety that the present environment is unlikely to be optimal, and that the environmental inadequacy is likely to be due to what may be referred to as discords. For reasons pointed out above, I shall concentrate on putative anxiety promoting discords early in life.

It is well documented that stressful conditions for infants, such as abuse or separation from mother, can lead to anxiety-related disorders in both humans and animals [35–38]. However, the prevalence of anxiety-related problems in humans appears to be much higher than the prevalence of serious child abuse or deprivation, and most patients do not seem to have that sort of background. Moreover, it has been shown that also brief separations elicit a distinct HPA response [39], and that there is a window of development in which such stressful events can predispose for fear and stress-related problems later in life [40,41], a predisposition presumably due to the augmentation of fear-related structures. Thus, even in the case of what is presently considered a normal upbringing, there may be a tendency to overstimulate the fear function to the extent that a considerable fraction develop anxiety problems. If so, the important question is what sort of discords are responsible?

One candidate discord concerns the way we care for infants. Presumably, Stone Age people would always stay in close proximity to the child, carrying it around at daytime, and sleeping next to it at night, as tribal people tend to do today [42]. In modern societies, the infant typically spends

much time without a sensation of where the parents are, as exemplified by sleeping arrangements. We typically put the infant in a separate room, or at least in a separate crib. If children cry when put to bed, a dominant line of thought has been that it is best to ignore their crying in order to teach them to sleep alone [43,44]. Following this advice, the baby will eventually stop crying, but the situation may, over time, spur excessive development of the fear function. Activation of fear, particularly of the branch referred to as separation distress, may also follow as a consequence of other aspects of modern living, such as the use of daycare centers. It is important to note that the question is not whether the environments the babies are offered are hazardous, both daycare centers and modern housing may very well be more safe than Paleolithic camp sites. The point is that the child may be prone to respond to the absence of parental proximity as a danger.

Another relevant mismatch concerns the amount of skin to skin contact the infants receive. In the Stone Age, there would be limited use of clothing, and more handling and carrying against the body [45]. In the absence of commercial substitutes, there was also more breastfeeding. Nursing is associated with higher cognitive scores and improved scholastic performance [46], and skin to skin contact in general is known to calm people [4,47]. Thus, a decrease in the dose of either nursing, or other forms of skin to skin contact, may contribute to anxiety disorders.

As to the handling of infants, it has been shown that rat pups receiving suboptimal care from their mothers will subsequently offer less care to their own offspring, and that this decrease in maternal care appears to be related to epigenetic changes [48,49]. More specifically, it appears that a less than optimal amount of licking and grooming triggers DNA methylation that reduce the activity of the glucocorticoid receptor gene. Rats with fewer glucocorticoid receptors are less tolerant to stress. Apparently, the reduction is also instrumental in changing the behavior of female rats in the direction of being more indifferent to their own infants. In other words, neglecting the infants have, at least in rats, an impact on the quality of maternal care in subsequent generations.

The present social setting is possibly one of the worst discords as to the impact on mental functions, affecting both infants and adults [19]. The close-knit tribal world of the Paleolithic has been replaced with the nuclear family and a large number of more or less unknown and unrelated people. There are several aspects of present social life that may be relevant in connection with anxiety, for example, being required to interact with strangers can stimulate the fear function. Fear of strangers is among the types of fears that appear to manifest spontaneously in infants at an early age [50].

One might argue that the fear function was activated as often in the Paleolithic as it is today due to the dangers that were either more common then, such as snakes and predators, or more dangerous then, such as infections and bad weather. However, these would be the type of fearful situations for which evolution has prepared us. Present fear stimuli may, or may not, be more common, but they are at least qualitatively different (the term 'qualitatively' here refers to both the type of stimuli and the differences in the relative frequency or intensity of stimuli). The evolutionary design of the human fear function may have rendered us less well equipped to handle the present situation [51]. For example, in the Paleolithic tribes, the long-term, close relationship between individual members possibly helped resolve conflicts at an earlier stage. Social interactions are assumed to be an important contributor to current stress-related problems [51–53].

Research that may substantiate proposed discords

To the extent that the problem of anxiety is due to discords in the modern environment, it is important to conduct research to find these discords and estimate their relative importance. The above suggested discords may be evaluated by epidemiological methods, either by comparing cultures with different practices or by correlating anxiety with various childhood experiences within a culture. However, confounding factors are an important problem of cross-cultural comparison, while the homogeneity of child caring practices in modern societies (with the exception of gross deprivation or abuse) limits the latter approach. Ideally, one would wish to obtain data by long-term follow up of children in a population that does differ sufficiently in handling infants.

A mother–infant cohort study, referred to as The Norwegian Mother and Child Cohort Study (MOBA), has recently been initiated at my institute. The study aims at recording some of the relevant parameters as to childcare practice, and to follow the infants in order to evaluate their health at various stages in life. As a large scale prospective study, it should offer relevant data, but it will take many years.

Several cross-cultural comparisons of anxiety have been published [54–56], but the cultures investigated tend to be industrialized, and therefore do not reflect the original child baring practices of Paleolithic people. As to the rare tribal cultures that still might come close to such practice, the problems are: one, that the instruments designed to evaluate anxiety are not easily applicable; and two, that these populations have been squeezed into marginal environments with concomitant stress factors, including the exposure to industrialized society.

One strategy for obtaining relevant data does not appear to have been fully exploited. Instruments used to assess anxiety, such as part of the General Health Questionnaire [57], or a short form of the Symptom Check List discussed in Ref.[58], may be combined with questionnaires to the subjects and/or their parents that reflect the discords suggested above. The questions should include topics such as sleeping arrangements, the amount of skin-contact,

breastfeeding, whether the baby was carried around, and the use of babysitters or kindergarten. A study along this line is in preparation. Depending on funding, the study will be performed in different cultural settings, allowing for the comparison of cultures that tend to have variable practices as to childcare. Ideally, the study will include some five to 10 different settings, including both urban and rural industrialized populations, as well as more traditional small-scale cultures.

If the suggested discords do contribute to anxiety, their individual impact may be limited, thus one would need a relatively large population in order to quantify the contribution. However, even if their individual impact is low, they apply to a large fraction of the present world population. Thus, their combined effect on anxiety-related problems may be substantial.

Conclusion

Although fear is an important innate function, one would expect that in the absence of causative environmental factors, fear should only rarely develop into a pathological and disabling feature. I suggest the following evolutionary medicine-based model for explaining the present pervasiveness of anxiety-related problems:

(1) The fear function is designed to be easily activated, which makes it particularly vulnerable to discords, in the form of excessive or abnormal activation, and to subsequent dysfunction.
(2) Anxiety is coupled with negative sensations, excess activity is therefore likely to reduce life quality. Moreover, due to the impact on a variety of bodily and mental functions, in the more overt cases, it can cause secondary ailments, particularly stress-related diseases.
(3) Like many other human functions, fear is designed to develop through interactions with the environment, particularly early in life.
(4) Modern living typically involves discords in the form of increased, and/or qualitatively different, stimulation of the fear function during infancy, which may cause the function to expand or in other ways develop inappropriately.
(5) Stress and anxiety later in life may amplify the problem.

While it is easy to substantiate that excessive anxiety is a problem causing considerable morbidity and loss of life quality in present societies, it is difficult to prove that the situation is due to particular discords. Neither is it possible to know whether Paleolithic people really suffered less. However, whether or not this was the case, one may be able to reduce the present prevalence by improving the environment. Reducing the amount of fear-inducing situations for infants may possibly contribute to this end.

While some issues are difficult to deal with, such as the social fabric of industrialized societies, one may be able to influence how children are cared for. More specifically, sleeping arrangements, breastfeeding, and the amount of skin-to-skin contact or carrying of the baby may have an impact on adult anxiety. Further research is needed, however, in order to substantiate up to what extent these factors really matter.

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