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LETTER

An Emerging Natural History in the Development, Mechanisms and Worldwide Prevalence of Major Mental Disorders

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Abstract: Conciliating recent findings from molecular genetics, evolutionary biology, and clinical observations together point to new understandings regarding the mechanism, development and the persistent worldwide prevalence of major mental disorders (MMDs), which should be considered the result of an evolutionary downside trade off. Temperamental/trait variability, by facilitating choices for individual and group responses, confers robustness flexibility and resilience crucial to success of our species. Extreme temperamental variants, originating evolutionarily from the asocial aspect of human nature, also constitute the premorbid personality of the disorders. The latter create vulnerable individuals out of whom some will develop MMDs but at much higher rate to that of the general population. Significantly, similar temperamental “lopsidedness” enables many of these vulnerable individuals, if intelligent, tenacious, and curious, to be creative and contribute to our survival while some may also develop MMDs. All have a common neural-developmental origin and share characteristics in their clinical expression and pharmacological responses also expressed as mixed syndromes or alternating ones over time. Over-pruning of synaptic neurons may be considered the trigger of such occurrences or conversely, the failure to prevent them in spite of it. The symptoms of the major mental disorders are made up of antithetical substitutes as an expression of a disturbed over-all synchronizing property of brain function for all higher faculties previously unconsidered in their modeling. The concomitant presence of psychosis is a generic common occurrence.

Keywords: Major mental disorders, Schizophrenia, Bipolar affective disorders, Obsessive compulsive disorders, Anxieties, Psychopathology, Molecular genetics, Evolutionary biology.

The combined 6% lifetime prevalence of MMDs worldwide, published by National Institute of Mental Health and for schizophrenia by Saha [1] irrespective of culture is a puzzle. Given the low procreation rate of the sufferers from MMDs [2], the disorders ought to be extinct or on the wane, obeying evolutionary forces weeding out an unproductive phenotype. Nevertheless, the prevalence is stable, persistent, and unaffected by cultural influences, except in the content of the occurring delusions colored by the local culture. The question arises as to what is keeping the rate stable. The answer may very well be hiding in plain sight, as we are forced to consider that there exists an evolutionary advantage associated with the events and prior developments - to be considered later - which may also end up leading to the unfortunate occurrence of the disorders as an unavoidable evolutionary, down, trade-off. Promising answers as to how this happens may be gleaned from recent findings from molecular genetics [3 - 9], evolutionary biology [9 - 12] and clinical observations [13 - 15]. Significantly, these findings when considered together, point to mechanisms for their development [16]:

1. Currently, temperament/ personality traits, as variously addressed in the numerous studies in psychology, sociology and psychobiology, lack a common language, uniform definitions, or point of reference in their studies to be useful in this matter. For our purpose, temperamental traits, based on recent evidence from evolutionary biology suggest that the inborn, behavioral propensities/traits - some of which, in interaction with the environment, are completed in their expression shortly after birth (*i.e.*, the ability to form bonds with others)

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- [17] - together with an acquired ethos and attitude, especially in early life, constitute one's final and enduring personality. The normally occurring temperamental variability, confers robustness, tenacity and flexibility in the choice of responses for a given situation, as well as resilience, not necessarily to the individual, or him alone, but to our entire species as a whole [11, 14] having survival value. A particular temperamental clustering which is termed premorbid personality, following the expression of the disorders, creates a pool of vulnerable individuals - some of whom may develop MMDs at a much higher rate to that of the general population. It originates mainly - *albeit* in its extreme form for this particular group - from evolutionary pressures on the individual [18]. According to the findings of E.O. Wilson and his co-workers, as mentioned above, such clusters of traits normally comprise one part of human nature. He proposed that the second one originates from evolutionary pressures on the social aspects of human experience such as empathy, connectedness, altruism, mutuality, cooperativeness, and tribalism *i.e.*, forming tribal identity and cohesiveness maintained by shared beliefs and practices and the sense of exclusivity felt by its members - all part of eusociality for our species [9 - 11]. Normally, as Wilson explains, we balance traits that are un-amalgamated, and chimera-like. This makes us successful though conflicting social animals. He further states that we exist in uneasy compromises between ourselves and those close to us within our own tribe and the adjoining ones.
2. There is evidence [19], the temperamental phenotypes that tend to originate mainly from the part of evolutionary pressures on the individual and which are made up mainly of asocial components such as autonomy, inner-directness, selfishness, calculative-ness, and aversion for social interactions and connectedness, with concomitant dearth of empathy, altruism and cooperation - *albeit*, in their extreme form for the phenomena we address, create a pool of vulnerable individuals, out of which some probabilistically will develop MMDs at the combined rate of +/- 6% for the worldwide general population [18, 20]. These particular, "lopsided" temperamental phenotypes while invariably constitute the premorbid personality of the sufferers- completely ignore their significance in our studies. They are also present in individuals who although vulnerable in developing the disorder, yet, do not. Significantly, this personality/temperamental configuration has a small variability within this group, which can explain the different versions of the expressed syndromes, as well can explain the polygenic origin of schizophrenia shown in the studies [21]. In the recent past, this disorder was believed erroneously as being caused by environmental, especially early childhood, experiences. Its variant forms are termed together as schizophrenic reactions. There was even a coined term of a "schizophrenogenic" mother! Such view has been persisted for decades. The worldwide persistent prevalence of 1-2% of the disorder, irrespective of culture, discredited this view. Recent evidence from molecular genetics considers its occurrence as mainly of genetic origin with some possible environmental factors that may act as precipitating triggers [21].
 3. The first expression of MMDs, especially in schizophrenia, occurs around late adolescence, being possibly precipitated by hormones as well as by social pressures particular for that age period. Steve McCarroll of Harvard and his associates have recently found [18] that among the genes associated with the development of schizophrenia, one hundred normally tagged pathogens in the body exist for removal by the immune system. A particular gene out of this implicated group, named *c4* and its variants, in the brain are associated in the case of schizophrenia, in over-pruning of neurons. Such an event is especially heightened at the end of adolescence, the very time when the disease mainly expresses itself. The obvious supposition; the overactive *c4* and its variants may somehow be responsible by this over-pruning in triggering the occurrence of schizophrenia. On the other hand and conversely, we should also consider the opposite: that the 1-2% prevalence, in the case of schizophrenia, may be due to the failure of the *c4* to prevent it, in spite of the over-pruning! The *c4* (and its variants), being a regulatory gene, may successfully prevent the very occurrence of the disorder for the majority of vulnerable individuals by its stated over-pruning, thus safeguarding temperamental variability. This consideration is bolstered by the existence of many individuals whose temperamental traits conform to the premorbid personality of those that do develop the disorder, yet do not themselves. We should also consider that the gene *c4* and its variants become overactive at that time, responding to an underlying particular synaptic layout of certain individuals which is expressed phenotypically in them before the occurrence of the disorder as a "lopsided", temperamental variant, which also constitutes characteristically the premorbid personality of the disorder. The latter, as mentioned, originates mainly from the asocial aspects of human nature *albeit*, in various configurations. The characteristics of these "lopsided", temperamental traits have not been the subject of our scrutiny as to their significance for schizophrenics constitute the premorbid personality mentioned above. They are: aloofness and self-absorption with notable dearth of social attributes such as an aversion to connectedness and a cooperation and lack of empathy or altruism [19, 20]. These individuals are often able to mask these with learned civility or emotional effusiveness. The felt, inner void, and even boredom by the patients are the result

of the asocial nature of their temperament. The sufferers being a kind of “a commonwealth of one!” to use an oxymoron metaphor - readily admitted if asked. Importantly though, the individuals with these particular, “lopsided”, temperamental variants who are free from the constraints and burden of social algorithms, also are now enabled, if also tenacious and intelligent, to be creative, to think in alternatives, and invent novel solutions to given problems, including discerning applicable properties of phenomena beyond the evolutionary normal limits of our comprehension - like quantum mechanics - thus contributing greatly to the survival of our species [22].

4. The particularly underlying, synaptic, layout expressing the mentioned temperament, may trigger a vigorous response of pruning by the regulatory c4 gene, by either of the two, possible mechanisms mentioned above. This event by creating a criticality, for some of these individuals, results in altering the overall, coordinating and synchronizing property of brain function [14, 15]. This crucial property - while not being previously taken into account in the modeling of the disorders - normally insures synchrony and the smooth, subtle expression of all higher, mental faculties, such as orderly thinking, coordinating of thinking with feelings, and appropriateness of social responses, all characteristics of normally functioning humans. In using a metaphor; this property in its expression, is reminiscent to the elegant synchronous waves of murmuration of a flying flock of starlings [23]. In the case of schizophrenia, during its first occurrence or subsequent relapse, this synchronizing property, switches to that of “a pathologically ordered state” of 'either/or', with spastic, uncoordinated expressions characterized by antithetical substitutes [24]. Examples of such substitutes are, the 'either/or' concrete-tistic thinking, the ambivalence, (*e.g.*, the presence of concomitant opposite feelings towards a person or an idea), apathy punctuated by explosive behavior, the non sequitur thinking (*i.e.*, faulty Association), the mismatch of feeling with thinking, and their inappropriate responses towards a given social situation and the feverish activity replaced by prolonged apathy, as well as inability to accommodate ambiguity. A kind of a “Psychic Parkinsonism” [24], Andreasen calls it “dysmetria” [25] - all characteristic of schizophrenia as well as the rest of MMDs, namely bipolar disorder involving the normal, smooth, mood modulation, expressed now with an either/or, manic-depressive, antithetical substitutes which contaminate judgment and decisions as well as cause erratic actions. It is important to note that the apparently mono-polar, major depressions (MDs) are in fact bipolar disorders where the depressive phases are markedly prominent while the manic ones are felt in the past by the sufferers, as merely mild transient “emotional rush”, hardly noticed but readily admitted by them if asked. In addition, chronic dysthymia with their occasional worsening due to adversities may be often erroneously diagnosed as MDs. For the obsessive compulsive disorder (OCD), involving the normal algorithmic faculty of sequencing scheduling and fore planning - an overlooked and unnamed faculty- now becomes expressed as stubbornness *versus* equivocation, fastidiousness alternating with slovenliness, entrainment of ideas and difficulties to bring closure to a decision. These phenomena are akin to the ensuing cacophony following the sudden departure of a conductor at an orchestra during a performance. The concomitant presence of psychosis, particularly in schizophrenia with its delusions and hallucinations is similar to those occurring as many assaults of brain function such as high fever, toxic shock, brain trauma, and heart surgery, along with many others. They should be considered an integrative attempt by the brain to react to a disruption in its functions. Meanwhile, all, whether they are part of a MMD or due to a physical assault on the brain, also respond to antipsychotic medications [25]. In addition, the initial expressions of mental disorders easily revert to a normal coordinating synchronizing function, with the application of electroconvulsive therapy (ECT), akin to that of atrial fibrillation which initially responds to electric shock, but, later becomes permanent and impervious to it. Following the ECT, the underlying premorbid personality remains unaltered.
5. We should now consider the occurrence of an extreme temperamental “lopsidedness” which, as mentioned above, originates mainly from an asocial aspect of human nature, while incurring vulnerability for the expression of the disorder. It is also freeing up a significant part of such an individuals' brain power that normally is taken up by the algorithms expressing the above - mentioned attributes of sociality. This creates a group of individuals who now unshackled from the confines of a social algorithm - if also tenacious and intelligent - become free to think in alternatives, create more encompassing scientific paradigms and offer novel solutions to a given problem. Thus, enabling to be more creative, contribute significantly to the overall survival of our species. Those with disorders involving mood modulation - a disturbance expressed in bipolar affective disorder - tend to be very creative mainly in music, poetry, and the arts even though, generally, creative individuals are generally creative in multiple areas of human endeavor. The advantages outweighing the disadvantages of the occurring number of MMDs is an unavoidable downside, even though creative individuals may also, themselves incur MMDs. The grim expression of the disorder could be considered an evolutionary

unavoidable trade off. Approximately, 450 million sufferers of it exist for 7 billion people globally. The persistence of the prevalence of 1-2% of schizophrenia, unaffected by culture and being persistent instead of becoming extinct or wane - given the low fertility rate of schizophrenics, bolsters the above explanations as a robust, working hypothesis to model the disorder in new and promising ways. Thus, answering the so called, "Darwinian paradox". Indeed, according to Aristotle, "No great mind has ever existed without a touch of madness". Creative geniuses, do express such temperamental extremes of the particular kind mentioned above, often being labeled as peculiar, idiosyncratic, or outright "mad". Many researches have noticed the association of creativity with MMDs, but did not outright link the invariable presence of their "lopsided" temperament, as previously mentioned, as both a vulnerability for developing a MMD as well as the very factor enabling the expression of creativity in the presence of intellect, curiosity, and tenacity of purpose [26 - 28]. Temperamental lopsidedness should be considered as the enabling factor necessary for the expression of creativity as is argued in this paper. The list of such creative individuals - some of whom also expressed at least one of the disorders, is long: Isaac Newton, Nichola Tesla [29], Albert Einstein [30], Steve Jobs [31], Joseph Handel [32], Amadeus Mozart [33], Alexander the Great [34], Lewis Carroll [35], Abraham Lincoln [36], Winston Churchill [37], John Adams [38]- among many others. The list is long indeed.

CONCLUSION

The occurrence of MMDs should be considered a probabilistic event interwoven with the constituents of our human nature. It is an unavoidable, particular outcome originating from the normally occurring temperamental variability in human *albeit* in it's extreme asocial form. The occurring lopsided version originates from the asocial part of our nature; though it makes individuals vulnerable to developing the disorder, some do (2% x7 billion = results in 140 million schizophrenic sufferers; the price we have to pay in suffering and cost). Importantly, it creates also a pool of individuals who because of it are able to express creativity, crucial to the evolutionary success of our species. Some of these creative individuals may also develop the disorders. The benefits of creativity outweigh the downside of the disorder hence its stable prevalence at the 1-2% rate is an evolutionary down trade-off. (The recently discovered occurrence of over-punning in late adolescence is involved in triggering the disorder by either of the two opposing mechanisms. The expression of clinical symptoms with their antithetical substitutes is the result of an overall disturbed synchronizing property in brain function. The co-occurring psychoses are a generic phenomenon, similar to all others occurring as a result of various assaults on the brain. Clinical experience, observations, and treatments involving over twelve thousand patients spanning well over five decades provided the author an opportunity to discern the common patterns. They in turn provided guidance in conciliating with recent findings from disparate fields of human sciences into a rational robust hypothesis in the natural history of the development and mechanisms of these disorders. It also offers a bridge to the gap between the linearity and reductionism of biological science - which tends to be based "on facts beyond a reasonable doubt", as it were, and the meaning of their emergent clinical phenomena in their complexity, are gleaned, by necessity, from the "preponderance of the evidence", to complete the metaphor. It opens rational, new ways based on the presented evidence, for the development of a more accurate modeling of the MMDs, improving their prevention and more effective treatments.

Discussion: Viewing the natural history of MMDs, especially schizophrenia, the way outlined in this paper - based on the conciliation of presented evidence from disparate fields - not only will help us in explaining several conundrums, such as the polygenic nature of a disorder, the clinical variability of its expression, the characteristic symptoms made up of antithetical substitutes with their concomitant psychosis, and the occurrence of the frequent relapses and remissions at the early history of the disorder, but, most importantly, will explain the Darwinian paradox of it's persistence.

The study of these "lopsided", temperamental phenotypes will be very important not only in their association with creative individuals, making up the premorbid personality link them with genetics and the cluster of genes which presently are solely associated with schizophrenia and the rest of MMDs.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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