Title: The role of chemosignals in the aetiology of schizophrenia

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Abstract

This paper proposes a new testable hypothesis about the evolutionary origins of schizophrenia. Specifically, we suggest that schizophrenia is the result of a faulty freezing response to fear signals, which in turn is due to a change in the degree to which caregivers express fear signals to infants. These fear signals involve both visual and olfactory elements, principally facial expressions and pheromones. The disappearance of natural predators and other life-threatening dangers over the past 20,000 to 30,000 years has caused the pheromone fear signal to atrophy, with the result that facial expressions of fear are no longer paired with their natural identifier. Consequently, some infants are less able to recognize facial expressions of fear in their caregivers, and the freezing response is activated in inappropriate contexts.

The role of chemosignals in the aetiology of schizophrenia

Schizophrenia is a serious mental disorder typified by both cognitive and emotional symptoms. Recently, impairments in emotion recognition have received particular attention [1]. A better understanding of emotional deficits in schizophrenia could lead to new therapies and improve social functioning of those afflicted by the disease [2].

The impaired processing of emotional stimuli in schizophrenia has been investigated in both visual and auditory modalities [3, 4]. The focus on these two sensory modalities reflects the traditional assumption that humans communicate emotional states primarily through visual means (facial expressions, bodily postures, gestures, etc.), with auditory cues sometimes playing a supplementary role in emotional communication.

Evidence is now emerging, however, that humans may also communicate emotional states via chemical signals. Experimental work has demonstrated that fear chemosignals emitted by the sender can generate a fearful facial expression and sensory acquisition (increased sniff magnitude and eye scanning) in the receiver [5]. The response is specific to the signal; disgust chemosignals, for example, evoke a different reaction – principally a facial expression of disgust,

and sensory rejection (decreased sniff magnitude, target-detection sensitivity, and eye scanning). Researchers now hypothesize that normal communication of emotion involves the simultaneous activation of visual, auditory, and olfactory channels, establishing a multilevel correspondence between sender and receiver [5].

In this context, it is interesting to note that schizophrenics have difficulty identifying odors. Research suggests that impairment of olfactory identification is a premorbid marker of transition to schizophrenia, though it is not predictive of psychotic illness more generally [6].

So far, however, there has been no research exploring possible links between the well-known problems with olfaction in schizophrenia with the impairments in emotion recognition. The theory of schizophrenia developed by one of the authors suggests that this may be a fruitful line of inquiry [7]. This theory proposes that the origins of schizophrenia lie in the misrecognition by infants of facial expressions of emotion exhibited by caregivers. In particular, infants who go on to develop schizophrenia in later life may tend to mistake other facial expressions of emotion (especially anger) for the expression of fear. In other words, the child often thinks others, especially caregivers, are afraid, even though they are not. This hypothesis however does not explain why certain infants misread facial expressions, while others interpret them accurately. The new research on the communication of emotion via chemosignals may supply such an explanation.

We hypothesize that the proper development of the cortical structures that mediate the fear response requires exposure to fear chemosignals during a certain critical period in infancy. This would be an example of the developmental priming mechanisms posited in General Systems Theory and applied to two-generational early intervention programs [8]. According to this theory, insufficient exposure to various developmental priming mechanisms are hypothesized to negatively affect developmentally appropriate cortical neuronal connections and synaptic efficiency associated with cognitive, linguistic and social development.

In the case of the fear response, developmental priming by exposure to the relevant chemosignals would have occurred naturally in the ancestral environment, since caregivers were often afraid (of predators, for example) in the presence of their infants. The natural response of the infant when seeing the expression of fear on their caregiver's face, or when detecting the chemosignals associated with fear, would have been to freeze [9]. In the modern environment, however, it is much less common for caregivers to be frightened in the presence of their infants, and as a result fewer infants are exposed to fear chemosignals during the critical period. We propose that the neural systems responsible for fear consequently fail to develop correctly in these infants. They may freeze during the critical period, but not in response to fearful facial expressions; instead, they may startle in response to an angry facial expression, and this may cause their fear system to "wire up the wrong way." From then on, the infant may be more likely to mistake other negative facial expressions, such as expressions

of anger or sadness, as expressions of fear, and as a result may freeze far more frequently than other infants. Our hypothesis predicts that these infants would be at risk of developing schizophrenia in early adulthood, and the frequent repeated freezing in response to misrecognition of emotional expressions of caregivers should play a key role in the aetiology of the disease. Our hypothesis also predicts that infants who do not mistake other facial expressions for expressions of fear during the critical period, either because their fear system has been correctly primed by exposure to fear chemosignals, or because they are born blind, will not be at risk of developing schizophrenia. Those infants who lack the genes responsible for the development of the freeze response will also be immune to schizophrenia.

To locate the cause of schizophrenia in infancy, as we propose, is not to deny the crucial role that adolescence seems to play in precipitating the first onset of the disease. Recent research suggests that abnormal brain maturation during adolescence may play a key role in the aetiology of schizophrenia. As teenagers' brains mature they go through a developmental stage called pruning, in which they lose synapses. Post-mortem studies show that people with schizophrenia have fewer synapses, which suggests that some of the mutations associated with the disease may cause too much pruning during adolescence [10]. Our theory complements this suggestion, in that it attributes the specific pathological consequences of over-pruning to the early developmental abnormalities in infancy. To use a metaphor, a ticking time-bomb is primed in infancy, but the clock is only set running in adolescence.

Schizophrenia is, according to our theory, a pathology of the fear system. The increasing safety of human environments over the past centuries has led to a decline in the frequency in which infants are exposed to fear chemosignals. Evolutionary theory predicts that this should have led the freezing response to atrophy, with the result that only a minority of infants inherit the full complement of genes for a fully functioning freeze response. It is to these genes that we should look for genetic associations with schizophrenia.

If this is correct, it would explain why the prevalence rate of schizophrenia is only around 1 per cent, if we suppose that less than 20 per cent of the population retain the full complement of genes required for a fully functioning freeze response, and only around 5 per cent of these people freeze "mistakenly" (i.e. in response to facial expressions of anger) with sufficient regularity to trigger pathological neurodevelopment.

PREVENTING SCHIZOPHRENIA

One important implication of our hypothesis is that it suggests a way to prevent the occurrence of schizophrenia. If schizophrenia is due to the infant mistaking other facial expressions of emotion for the expression of fear, and if this is due to the lack of exposure to the fear chemosignal during a critical period, then it follows that schizophrenia will not develop under the following conditions:

(1) If the infant is blind, it will not perceive any facial expressions of emotion on the part of the caregiver. It will therefore not misperceive any such facial expressions. It follows that congenital blindness will prevent the development of schizophrenia.

(2) If the infant is born without the full complement of genes required for a fully functioning freeze response, it will never freeze in response to any facial expression of emotion, whether this is the appropriate one (fear) or not (eg. anger, sadness). It will therefore not come to associate inappropriate facial expressions with the freeze response, and will not therefore be at risk of developing schizophrenia.

(3) If the infant is artificially exposed to the fear pheromone during some critical period (which we estimate to be roughly between the second and fifth month after birth, i.e. during the initial rapid growth of synaptic connections between neurons), then its ability to recognize facial expressions of fear should be primed in advance of visual acuity and it will be protected against schizophrenia.

There is some evidence that (1) is indeed the case; people born blind do not appear to suffer from schizophrenia [11]. Experiments are needed to test predictions (2) and (3). It will not be possible to test prediction (2) until we know which genes are required for a fully functioning freeze response. It should, however, be possible to test prediction (3) today. This would involve selecting MZ twins with a high genetic risk of developing schizophrenia, and exposing one of each pair at regular intervals between the second and fifth month after birth to the fear pheromone in spray form, whilst seeing an image of a fearful face. The pheromone required is taken from the Human alarm pheromones identified at Stoney Brook and defined in the patent application listed in the declaration of competing interests below. Following each exposure the infant is comforted and hears laughter, or is tickled until it laughs. The other twin is not treated, since it would be unethical to expose it to angry or sad faces without the hope of a corresponding benefit. The progress of the subjects is then monitored using the latest techniques.

We appreciate that the hypothesis advanced here may sound far-fetched, but it is compatible with the best current scientific evidence, and explains a number of puzzling features about schizophrenia, as well as suggesting a possible preventive treatment.

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Declaration of competing interests

Derek Goldsmith, "Method and substance for improving the emotional development of an infant," United States Patent Application no. 14/44,379