Childhood predictors of states of anxiety

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Development of the characteristics of social phobia often requires a diathesis in the form of a temperamental bias. A behavioral profile marked by vigorous motor activity and crying to unfamiliar stimuli at 4 months of age—called high reactivity—is characteristic of about 20% of healthy, Caucasian infants. This pattern predicts shy behavior in preschool children and symptoms of social anxiety at age 7, and, at age 11, a subdued personality and biological features that are consonant with a hypothesis of amygdalar excitability. The biological variables that best characterize the children who had been high-reactive infants are right-hemisphere activity in the electroencephalogram (EEG), a larger evoked potential from the inferior colliculus, higher sympathetic tone in the cardiovascular system, and larger event-related potentials to discrepant stimuli. About a quarter of 11-year-olds who had been high reactives displayed behavioral and biological characteristics that are in theoretical accord with the hypothesis of amygdalar excitability, while only 1 of 20 displayed a profile characterized by features in opposition to their temperament. The evidence points to a modest temperamental contribution to the development of symptoms currently regarded as diagnostic of social phobia.

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There is now a consensus that chronic possession of any one of the categories of anxiety disorder is most likely for individuals who inherit a temperamental diathesis.[1] The evidence used to infer a state of anxiety in humans can include verbal report, observed behaviors, or physiology. These three categories of evidence are not highly correlated and, therefore, the meaning of "anxiety" inferred from one source of information is not equivalent to the meaning inferred from a different source. It is important, therefore, to distinguish among four different concepts.[2]

Judged anxiety refers to verbal statements, on questionnaires or interviews, describing tension, uncertainty, or worry. However, had physiological measures been gathered on these individuals, they would not show the expected physiological accompaniments to their verbal statements. *Constructed anxiety* refers to a verbal report of anxiety that is accompanied by a physiological profile, but not the profile scientists assume to be theoretically appropriate. For example, an individual with an infection might feel tense and, in an attempt to understand this feeling tone, might decided that he or she is worried. *Physiological anxiety* refers to activation of the amygdala and its projections in individuals who do not report conscious feelings of anxiety. The fourth construct is the one most clinicians and scientists seek to measure. The individual reports feeling worried, tense, or anxious and, in addition, displays the physiological features that should accompany those feelings, including asymmetry of activation in the electroencephalogram (EEG) or high sympathetic tone.

Some individuals inherit a temperament that renders them especially vulnerable to the latter state of anxiety. This temperamental bias is regarded as a diathesis for the development of one or more of the psychiatric anxiety

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disorders.[3] It is assumed that these temperamental biases are influenced, in part, by heritable variation in the complex neurochemistry of the central and autonomic nervous systems. The relevant neurochemistry could include variation in γ-aminobutyric acid (GABA), corticotropin-releasing hormone, opioids, norepinephrine, and other molecules.[4]

Study design

Evaluation from age 4 months to 7 years

My laboratory has been studying longitudinally a large group of healthy, Caucasian children from middle-class families who have been followed from 4 months to 11 years.[4] Each infant was classified at 4 months of age into one of four temperamental groups based on their behavior to a standard battery of visual, auditory, and olfactory stimuli. Infants who showed a combination of frequent, vigorous motor activity combined with frequent crying were classified as high reactive (22% of the sample). Infants who showed the opposite profile of infrequent motor activity and minimal crying were classified as low reactive (40%). Infants who showed infrequent motor activity, but frequent crying were classified as distressed (25%), and infants who showed frequent motor activity, but minimal distress were classified as aroused (10%). It is assumed, but not yet proven, that the high- and low-reactive groups inherit different profiles of excitability in the amygdala and/or bed nucleus and their projections. These temperamental groups are regarded as categories rather than a continuum of reactivity.

The children from these temperamental groups were evaluated twice in the second year for their reaction to unfamiliar people, situations, and procedures. The 14- and 21-month-old children who had been categorized as high reactive as infants were more likely than the low reactives to display high levels of fear to unfamiliar people, rooms, and events.[4] This relationship has been verified by Fox and colleagues,[5] who also found that 1-year-olds who had been classified as high-reactive infants at 4 months were more fearful than others when they encountered unfamiliar events.

These children were observed when they were four and a half years old in a play session with two other unfamiliar children of the same sex and age, while the three mothers sat on a couch in the playroom. Each child was classified reliably as inhibited, uninhibited, or neither, based on their behavior with the other children and their reactions to two unfamiliar events that occurred after the play session. Significantly more high than low reactives were classified as inhibited. They were quiet, spent long times close to their mother, and did not initiate social interaction with the other children.

When the children were seven and a half years old, we evaluated the prevalence of anxious symptoms in 51 high reactives, 60 low reactives, and 53 children from the other two temperamental groups. The classification of anxious symptoms, which included extreme shyness, worry about the future, fear of thunderstorms, animals, or loud noises, recurrent nightmares, and occasional reluctance to go to school, was based on questionnaire and interview data with the mother and the child's teacher. A total of 43 of the 164 children met criteria for possession of anxious symptoms. Forty-five percent of the children who had been high-reactive infants, compared with 15% of low reactives, had anxious symptoms (chi-square=12.8, $P<0.01$).[6] High reactives who had anxious symptoms were more fearful in the second year and had higher sitting diastolic blood pressures and a greater magnitude of cooling of the temperature of the fingertips across a series of digit recall problems, compared with other high reactives. Cooling of the fingertips is the result of sympathetic inervation of the arteriovenous anastomoses under the surface of the skin.

Evaluation at age 11 years

These children were evaluated most recently when they were 11 years old. The 3-hour battery consisted of both behavioral and biological assessments. The behavioral data included the number of spontaneous comments and smiles displayed toward the examiner during the first 18 min of interaction, a reliable rating (4-point scale) of the degree of uncertainty, tension, and anxiety displayed by the child in this setting, and a maternal Q-sort of 28 items describing the child's behavior.

Four different classes of biological variables, each under the potential influence of the amygdala, were also quantified. These biological variables were: (i) asymmetry in the magnitude of desynchronization of alpha frequencies in the EEG; (ii) magnitude of the evoked potential from the inferior colliculus to a series of clicks; (iii) sympathetic tone in the cardiovascular system; and (iv) the magnitude of the wave form at 400 ms in the event-related potential to discrepant visual scenes.

Most children and adults have less alpha power in the left than in the right frontal area when at rest, suggesting greater activation of cortical pyramidal neurons in the left frontal lobe. Further, individuals with this EEG profile report more sanguine moods and fewer signs of anxiety than the smaller proportion, who show greater activation on the right side.[7] The amygdala sends ipsilateral projections to the frontal lobe through the basal nucleus of Meynert and it is likely that these projections contribute to the asymmetry in the alpha band of the EEG. A child who had greater activation in the right amygdala should show greater desynchronization of alpha frequencies in the right hemisphere and would be classified as right hemisphere active.

The brain stem auditory evoked response (BAER), elicited by a series of clicks delivered through earphones, was a relevant measure because variation in the magnitude or latency of the fifth wave in the BAER response—called "wave 5"—differentiates between personality and clinical categories.[8-11] In addition, adults with panic disorder show a larger wave 5 than do controls.[12] The peak of the fifth wave is believed to represent the termination of the lateral lemniscus on the inferior colliculus.[13] The theoretical relevance of this fact is that the amygdala projects to the inferior colliculus through both the central gray and the locus cereleus and, therefore, children with a more excitable amygdala should display a larger wave 5 than others.[14]

The rationale behind recording the event-related potential to discrepant visual stimuli derived from the assumption that the amygdala reacts to discrepant or unexpected events and projects to cortical neurons that mediate the event-related potential.[15] If high reactives possess a low threshold of reactivity in the amygdala and its projections, then they should show a larger event-related potential to discrepant events. The usual wave form to a discrepant event occurs between 150 and 800 ms with a peak between 300 and 400 ms. Preadolescent children most often show a negative wave form that is called Nc (for negative component).[16]

Each child was presented, through goggles, two series of pictures with 169 pictures in each series. In the first series, 70% of the pictures were of the same item (a fireworks display), 15% were of the same flower, the oddball stimulus, and the remaining 15% were each different, but ecologically valid (a chair or kitchen utensil). These pictures were called novel valid. In the second series, the frequent picture presented 70% of the time was a yellow fire hydrant, the oddball stimulus was a different flower, and the remaining fifteen percent of the pictures were each different, but ecologically invalid (for example, a chair with three legs). These pictures were called novel invalid.

Finally, we recorded measures of cardiovascular activity as an index of reactivity in the sympathetic nervous system. The amygdala sends varied projections to the sympathetic system and, therefore, we assumed that high reactives would show signs of greater sympathetic reactivity than low reactives.[17]

The two major variables were the ratio of high- to low-frequency power in the cardiac spectrum while the child was laying supine. A fast Fourier transformation of the distribution of beat-to-beat differences in the sample of resting heart rate usually reveals two peaks in the distribution. The higher frequency, around 0.2 Hz, represents the parasympathetic influence of respiration on heart rate–vagal tone. The lower frequency band, from 0.02 to 0.10 Hz, represents both sympathetic and parasympathetic influences on heart rate, due to cycles of change in blood pressure and body temperature. Higher relative power in the low frequency band is usually correlated with a high resting heart rate and is indicative of higher sympathetic tone.[18]

Results

Behavior

The high-reactive children were more subdued and anxious at the 11-year evaluation than the low reactives and were rated as more anxious and inhibited during the first 18 min of the interview *(Table I)*.

Rating	Low reactive	High reactive
1 (relaxed, uninhibited)	50%	22%
2	28%	22%
3	8%	22%
4 (maximally anxious, inhibited)	14%	34%

Table I. Percentage of high and low reactives receiving ratings of 1, 2, 3, or 4, while interacting with the examiner at the 11-year-old evaluation.

Twice as many high as low reactives were rated as extremely inhibited (rating of 4; awarded to children who made very few comments and smiles, displayed a great deal of motor tension, spoke in a soft voice, and

showed other signs of concern). Twice as many low as high reactives were rated as minimally anxious and uninhibited with a rating of 1, which described a maximally relaxed and spontaneous child (chi-square=11.8, $P<0.01$). Further, more high than low reactives had values for both number of spontaneous comments and smiles in the lowest quartile of the two distributions; more low reactives had values in the highest quartile for both measures (chi-square=4.2, $P<0.05$). Thus, the infant temperamental profiles predicted, to a modest degree, spontaneity or a subdued style with the unfamiliar adult examiner.

One half of the current group of high and low reactives had been seen when they were four and a half and seven and a half years of age. A similar rating of degree of anxiety/inhibition on a 4-point scale was assigned to each child based on 90 min of interaction with a different, but unfamiliar female examiner. Seventy percent of the low reactives, but only 13% of the high reactives were uninhibited at all three ages; 38% of high reactives, but only 6% of low reactives were inhibited at all three ages (chi-square=21.3, $P<0.001$). It was rare for a low-reactive infant to become a consistently inhibited child or for a high-reactive infant to become a consistently uninhibited child. As expected, the uninhibited profile was better preserved because family and friends encourage sociability and discourage shyness and timidity.

Seven descriptive items on the maternal Q-sort referred to shyness or sociability in the child. We computed the mean ranks the mother assigned to her child for the three shy and the four sociable items. High reactives were described as more shy and less sociable than the low reactives ($t(149)=3.91$, $P<0.01$).

Biological variables

Figure 1 illustrates the mean standard scores for high and low reactives on the four biological variables at 11 years of age: right parietal activation in the EEG, wave 5 magnitudes, sympathetic tone (a low ratio and a high resting heart rate), and the mean of the integrated voltages from 400 to 1000 ms for the event-related potential to the first oddball flower and the novel invalid scenes.

The high reactives had greater EEG activation at the right parietal site ($t(152)=2.53$, $P<0.05$). Further, the high reactives who had been highly fearful in the second year showed greater activation in the right frontal area compared with low reactives who were equally fearful in the

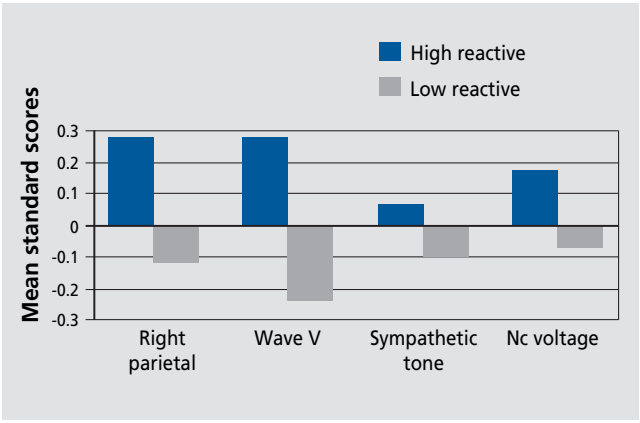

Figure 1. Mean standard score for four biological variables for 11-year-old children who were classified as high or low reactive at 4 months.

second year. The high reactives also had significantly larger wave 5 values ($t(125)=2.87$, $P<0.05$), and this variable best separated the two temperamental groups.[19]

The high reactives also had greater sympathetic tone in the cardiovascular system; 49% of high reactives, but only 32% of low reactives, combined a low ratio in the spectral analysis with a high resting heart rate; 32% of the low reactives, but only 16% of high reactives, combined a high ratio with a low resting heart rate (chi-square=4.9, $P<0.05$). It is also of interest that high sympathetic tone was the best correlate of behavior. The children with high sympathetic tone, compared to those with high vagal tone, spoke less often, were rated as more anxious, and were described by their mother as shy. Although the EEG, wave 5, and event-related potential data also separated the two temperamental groups, these measures were less closely related to the child's behavior.

One explanation is that sympathetic activity is likely to influence the orbitofrontal cortex, which mediates a conscious awareness of feeling tone. A rise in heart rate and blood pressure and a change in breathing results in information being sent to the brain through the medulla to provoke changes in the orbitofrontal cortex that can evoke an alteration in conscious feeling. A subdued mood and avoidance behavior can be consequences of this altered feeling tone. By contrast, activity in the inferior colliculus and the pyramidal neurons of the cortex are less likely to influence orbitofrontal neurons and, therefore, no change in feeling tone occurs and there should be a minimal relationship to behavior. It is important that among high and low reactives, who were equally

subdued in their behavior in the laboratory, only the high reactives showed the biological features of right parietal asymmetry and a large wave 5. The similar behaviors do not necessarily imply similar values on all biological variables. That is why it is important for investigators and clinicians to gather biological data to supplement their behavioral observations and interviews.

Finally, the high reactives had significantly larger Nc voltages to the first oddball picture and the novel invalid pictures ($t(136)=2.00$, $P<0.05$). Further, the correlation between the voltages and these two classes of pictures across frontal and parietal sites were always positive and significant for high-reactive children, but not for the low reactives. That is, only high reactives showed coherence in the magnitude of the Nc across disparate cortical sites, implying that the discrepant scenes recruited neurons over a broader cortical area.

There was an interesting asymmetry in the sensitivity of low compared with high values on the four biological measurements. Low values better differentiated low from high reactives than did high values, suggesting that it is easier for low-reactive than for high-reactive children to attain a state of low cortical and autonomic arousal, even though the former can attain, temporarily, a state of higher arousal in a laboratory setting. All animals must be biologically prepared to become aroused to threat or challenge. The psychological advantages of low arousal are less obvious and apparently a smaller proportion of individuals are able to reach a state of relaxation.

Prediction of states of anxiety

About 1 in 4 children who had been high reactive and 1 in 4 children who had been low reactive developed a behavioral and a biological profile at age 11 that was in accord with theoretical expectations, while only 1 of 20 children developed a profile of social behavior and biology that violated their expected profile. This result is of interest in light of the varied social experiences that these children have encountered over the prior 11 years. Most children displayed behavioral and biological patterns that were characteristic of randomly selected children from middle-class, Caucasian populations. Thus, the prediction that a high-reactive infant will not be highly sociable and exuberant, and show low biological arousal at age 11 can be made with much greater confidence than the prediction that this category of child will be extremely subdued and anxious, and show signs of high arousal in cortical and autonomic targets. The suggestion that a temperamental bias constrains development more effectively than it determines particular outcomes applies to environmental conditions as well. If all one knows about a group of 100 children is that they were born to economically secure, well-educated, nurturing parents and must predict the likely psychological adult outcomes, the most accurate guesses will refer to the profiles that should not occur: criminality, school failure, psychosis, homelessness, drug addiction, and poverty. Predictions concerning the more specific features that will be part of the adult personality are less likely to be validated. Each temperament eliminates many more possibilities than it determines. This principle holds for the cells of the young embryo. The final fate of a neural crest cell in a 3-week-old embryo, whether sensory ganglion, melanocyte, or a muscle of the heart, is less certain than the fact that this cell will definitely not become connective tissue or part of the reproductive system.

Conclusion

The evidence affirms the view that a temperamental bias for high reactivity in infancy, detectable early in development, is predictive of a personality profile marked by shyness, timidity, and anxiety to unfamiliar events and this behavioral phenotype is accompanied by a select biological pattern that implies amygdalar excitability. The question of greater relevance for clinicians is whether this category of child is at higher risk for any of the current psychiatric anxiety disorders. Preliminary evidence invites an affirmative reply. An independent group of 13-year-olds, who had been classified as inhibited or uninhibited in the second year, were interviewed by a psychiatrist who had no knowledge of their initial temperamental classification or later laboratory behavior. More of the adolescents who had been inhibited rather than uninhibited in the second year had symptoms of social anxiety (61% versus 27%).[20] However, these inhibited children were not more likely to have developed specific target phobias or separation anxiety, implying that inhibited children might be at special risk for the development of social phobia during the adolescent or adult years.

The feared target of the social phobic is concern over the evaluations made by unfamiliar people in unfamiliar situations. By contrast, the feared target of the phobic patient is a very specific object that can harm or conta-

minate the agent. The feared target of the panic patient is anxiety over an unexpected autonomic surge. The targets and physiological profiles of these three groups are different and probably comprise different psychiatric categories.

Two puzzles remain. First, 20% of the children were high-reactive infants, but the prevalence of social phobia is less that 10%. This fact suggests that many high reactives find an adaptive niche in their society that allows them to titer unpredictable social encounters. The biography of T. S. Eliot implies that he may have been a high-reactive infant, for he certainly was a shy child. His decision to become a poet permitted a degree of isolation that his temperament required.

The second fact is that more females than males are diagnosed with social phobia, although there is no excess of girls over boys who are classified as high reactive during infancy. This fact suggests that cultural ideals and differential socialization of boys and girls contribute to the sex difference in social phobia. Boys may try much harder to conquer their avoidance behavior and shyness. An excerpt from an essay written by one of the 11-year-old children, who was a high-reactive infant and a fearful toddler supports this claim.

I have always been more of an anxious person than some other people … it took me a very long time to realize how to cope with this heightened state of nervousness … I have also found that the manifestation of my anxiety can be overcome by using simple mind over matter techniques. A good example of this is when I was 8, after learning about what asthma was, I started to feel like I was having trouble breathing. In a heightened state of anxiety, I subconsciously forced myself into believing that I had asthma. This has happened many times. Besides just general fears, it was a struggle to overcome this anxiety manifestation. I overcame these problems, though. I know how to deal with them when they occur. Because I now understand my predisposition towards anxiety, I can talk myself out of simple fears.

It is also important to note that a high-reactive temperament protects the child from engaging in risky behavior—whether drugs, driving at high speeds, or temptations for delinquent behavior. Thus, the child with a high-reactive temperament has some advantages in our society and parents of such infants might decide not to change their child's behavior when the next set of pharmacological advances permits them that choice. ❑

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Predictores infantiles de los estados de ansiedad

El desarrollo de las características de la fobia social a menudo requiere de una diátesis que se basa en una predisposición del temperamento. Un perfil de conducta marcado por una actividad motora vigorosa y llanto ante estímulos no familiares a los cuatro meses de edad – llamado alta reactividad – es característico en cerca del 20% de los lactantes caucásicos sanos. Este patrón predice una conducta tímida en niños preescolares y síntomas de ansiedad social a la edad de 7 años, y a la edad de 11 años una personalidad reprimida y características biológicas que están en consonancia con una hipótesis de excitabilidad de la amígdala. Las variables biológicas que mejor caracterizan a los niños que han sido lactantes con alta reactividad son una actividad del hemisferio derecho en el electroencefalograma (EEG), un potencial evocado mayor desde el colículo inferior, un tono simpático más elevado en el sistema cardiovascular y mayores potenciales relacionados con eventos para estímulos discrepantes. Cerca de la cuarta parte de los niños de once años que han tenido alta reactividad desarrollan características conductuales y biológicas que están en concordancia teórica con la hipótesis de la excitabilidad de la amígdala, mientras que sólo 1 de 20 desarrolla un perfil caracterizado por rasgos opuestos a su temperamento. La evidencia apunta a una contribución modesta del temperamento al desarrollo de síntomas actualmente considerados en el diagnóstico de la fobia social.

Les facteurs prédictifs des états anxieux de l'enfance

Le développement des traits caractéristiques de la phobie sociale nécessite souvent un terrain à type de déviation du tempérament. Un profil comportemental caractérisé par une réactivité élevée (activité motrice importante et pleurs aux stimuli étrangers) à l'âge de 4 mois se retrouve chez à peu près 20 % des enfants d'origine caucasienne en bonne santé. Un tel schéma est annonciateur d'un comportement timide chez les enfants d'âge préscolaire et de symptômes d'anxiété sociale à l'âge de 7 ans et, à l'âge de 11 ans, d'une personnalité effacée et de caractéristiques biologiques compatibles avec l'hypothèse d'une excitabilité amygdalienne. Les variables biologiques qui caractérisent le mieux les enfants ayant eu une réactivité élevée sont l'activité de l'hémisphère droit sur l'électroencéphalogramme (EEG), un potentiel évoqué du colliculus inférieur augmenté, un tonus sympathique du système cardiovasculaire plus élevé, et des potentiels plus importants aux stimuli contradictoires liés aux événements. Environ un quart des enfants âgés de 11 ans ayant eu une réactivité élevée ont présenté des caractéristiques biologiques et comportementales qui sont en accord théorique avec l'hypothèse d'une excitabilité amygdalienne, tandis que seulement 1 sur 20 a montré un profil caractérisé par des manifestations en opposition avec son tempérament. Cet argument s'inscrit en faveur d'une contribution modeste du tempérament au développement des symptômes considérés actuellement comme permettant de porter le diagnostic de la phobie sociale.