U.S. Department of Health and Human Services
NIH News
National Institutes of Health

December 04, 2006

Brain's Fear Center Shrinks in Autism's Most Severely Socially-Impaired
Well Siblings Share Some of the Same Behavioral, Neural Features

The brain's fear hub likely becomes abnormally small in the most severely socially impaired males with autism spectrum disorders (http://www.nimh.nih.gov/healthinformation/autismmenu.cfm), researchers funded by the National Institutes of Health's (NIH) National Institute of Mental Health (NIMH) and National Institute on Child Health and Human Development (NICHD) have discovered. Teens and young men who were slowest at distinguishing emotional from neutral expressions and gazed at eyes least — indicators of social impairment — had a smaller than normal amygdala, an almond-shaped danger-detector deep in the brain. The researchers also linked such amygdala shrinkage to impaired nonverbal social behavior in early childhood.

The new findings suggest that social fear in autism may initially trigger a hyperactive, abnormally enlarged amygdala, which eventually gives way to a toxic adaptation that kills amygdala cells and shrinks the structure, propose Richard Davidson, Ph.D., and colleagues at the University of Wisconsin, who report on their magnetic resonance imaging (MRI) study in the December 2006 *Archives of General Psychiatry.**

In a related study, another research team led by Davidson found that well siblings of people with autism share some of the same differences in amygdala volume, and in the way they look at faces and activate social/emotional brain circuitry, particularly an area critical for face processing.

"Together, these results provide the first evidence linking objective measures of social impairment and amygdala structure and related brain function in autism," explained Davidson. "Finding many of the same differences, albeit more moderate, in well siblings helps to confirm that autism is likely the most severe expression of a broad spectrum of genetically-influenced characteristics."

While SOME people with minimal expression of these traits might be perceived as aloof or loners, those at the more severe end of the spectrum are unable to engage in give-and-take interactions and fail to develop age-appropriate peer relationships. Notably, they shy away from looking at eyes. Davidson's research team had reported last year linked such eye-gazing with hyperactivation of their fear hub.** Yet different studies have found the amygdala in autism to be variously enlarged, shrunken or even normal in size.

Davidson, Kim Dalton and colleagues suspected that these seemingly inconsistent findings resulted from the wide variability of the autism spectrum, which masked amygdala changes — that a clearer picture would emerge if the length and severity of hypersensitivity to social interactions were factored in. They brought to bear eye-tracking and other measures of facial emotion processing in combination with MRI to find out if degree of non-verbal social impairment might predict amygdala volume in 49 males, aged 8-25, including 25 with autism spectrum disorders.

Those in the autism group who had a small amygdala were significantly slower at identifying happy, angry, or sad facial expressions and spent the least time looking at eyes relative to other facial regions. Autistic subjects with the smallest amygdalae took 40 percent longer than those with the largest fear hubs to recognize such emotional facial expressions, and those with the largest amygdalae spent about four times longer looking at eyes than those with the smallest. Eye fixation did not correlate with amygdala volume among 24 control subjects. The size of the amygdala increased early in autism group subjects with normal eye fixation, while it increased little in those with low eye fixation. Moreover, autism group subjects with small amygdalae had the most non-verbal social impairment as children.

The researchers suggest that the amygdala in autism fits a model in which a brain structure adapts to chronic stress — in this case, fear of people — by first becoming hyperactive, but over time succumbing to a process of toxic cell death and atrophy, as has been proposed occurs in the hippocampus for some forms of depression.*** Children with autism who are least hypersensitive to interaction with people would thus show slower amygdala shrinkage while those who were most hypersensitive would begin to show amygdala changes early in life. Such amygdala adaptations likely affect most people with autism by adulthood, according to the researchers. However, they caution that these changes do not explain all autistic behavior, but account for slightly more than half of the variability in nonverbal social impairment.

In the related study, published online in Biological Psychiatry, October 24, 2006,**** Davidson, Kim Dalton, Ph.D. and colleagues at the University of Wisconsin employed functional magnetic resonance imaging (fMRI) as well as many of the same measures used in the above study in 21 subjects with autism, 12 siblings and 19 healthy controls. Notably, they found that unaffected siblings of people with autism showed a similar pattern of smaller amygdalae, and decreased eye fixation as their autistic siblings when looking at faces.

However, while the autism group showed reduced activation of a face-processing area, the fusiform gyrus, on both sides of their brains while performing a face-processing task, the well siblings showed this difference only on the right side. This suggested an "intermediate pattern" — that the well siblings were using circuitry similar to healthy controls, but with some slight changes reminiscent of their autistic siblings, but not as pervasive.

Similarly, eye fixation time did not predict amygdala activation in the well siblings as it did in their autistic relatives. This suggested that looking at faces did not boost activation of emotion-related circuitry in the well siblings. Looking at eyes may not be a negative experience for them, again suggesting an intermediate pattern. Nonetheless, their amygdalae were about the same size as those in the autism group.

The findings of both studies, taken together, suggest that measures such as eye gazing time may prove useful in clarifying the relationship between genes, brain and behavior in the autism spectrum, say the researchers.

Also participating in the Archives of General Psychiatry study were: Kim Dalton, Ph.D., Tom Johnstone, Ph.D., Micah Long, Emelia McAuliff, Terrence Oakes, Ph.D., Andrew Alexander, Ph.D., University of Wisconsin.

Also participating in the Biological Psychiatry study were: Brendon Nacewicz, Andrew Alexander, Ph.D., University of Wisconsin.

The Archives study was also funded by NARSAD. The Biological Psychiatry study was also funded by NARSAD and NAAR.

The National Institute of Mental Health (NIMH) mission is to reduce the burden of mental and behavioral disorders through research on mind, brain, and behavior.More information is available at the NIMH website, http://www.nimh.nih.gov .

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* Nacewicz BM, Dalton KM, Johnstone T, Long MT, McAuliff EM, Oakes TR, Alexander AL, Davidson RJ. Amygdala volume and nonverbal social impairment in adolescent and adult males with autism. *Arch Gen Psychiatry*. 2006 Dec;63(12).

** Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, Alexander AL, Davidson RJ. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci*. 2005 Apr;8(4):519-26. Epub 2005 Mar 6.

***McEwen BS. Mood disorders and allostatic load. *Biol Psychiatry*. 2003 Aug 1;54(3):200-7. Review.

****Dalton KM, Nacewicz BM, Alexander AL, Davidson RJ. Dalton KM, Nacewicz BM, Alexander AL, Davidson RJ. Gaze-Fixation, Brain Activation, and Amygdala Volume in Unaffected Siblings of Individuals with Autism. *Biol Psychiatry*. 2006 Oct 24; [Epub ahead of print]