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Research In Brief

February/March 2007 07-1

The Development of Aggression in 18 to 48 Month Old Children of Alcoholic Parents

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Abstracted from *Journal of Abnormal Child Psychology, 34,* 409-423, 2006.

This study examined the development of aggressive and oppositional behavior in children among alcoholic and nonalcoholic families. Questionnaires and observations were used to assess families. When the children were 18 months old, maternal and paternal reports of alcohol use were used to determine whether families would fit the "nonalcoholic," "father alcoholic," or "both parents alcoholic" groups of the study. Child aggression was assessed by parental reports at 18, 24, 36, and 48 months of age.

Findings

- Children in families with nonalcoholic parents had the lowest levels of aggressive behavior at all time points compared to children with one or more alcoholic parents.
- Children in families with two alcoholic parents did not exhibit the usual decreases in aggressive behavior that children in nonalcoholic families exhibited from ages three to four.
- Boys had higher levels of aggressive behavior at all ages than girls. Boys with two alcoholic parents had significantly less of a decline in aggression from three to four years of age when compared to boys with nonalcoholic parents.
- A high family risk factor (determined by combining a number of measures including parental depression, antisocial

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Long-term Reduction in Ventral Tegmental Area Dopamine Neuron Population Activity Following Repeated Stimulant or Ethanol Treatment

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Abstracted from *Biological Psychiatry, 61,* 93-100, 2007.

On this study, researchers used an animal model to examine the drug-induced changes in the brain that may be responsible for drug addiction. Two types of drugs of abuse were investigated: psychostimulants (specifically cocaine, nicotine, and amphetamine) and alcohol.

The electrical activity of midbrain dopamine neurons was studied long (three to six weeks) after the termination of repeated drug use. Dr. Shen's laboratory demonstrated for the first time that a persistent reduction in the electrical activity of these neurons followed repeated exposure to these drugs. Such a change parallels the persistent nature of addiction and could be an important brain mechanism underlying the cause of addiction.

Findings

- Repeated use of stimulants or alcohol led to a persistent or long-term reduction in the electrical activity of dopamine neurons after the termination of repeated drug exposure (i.e., three to six weeks post drug exposure). The reduced electrical activity was reflected in a reduction in the number of dopamine neurons expressing spontaneous impulse activity (action potentials).
- The reduced electrical activity in dopamine neurons after repeated exposure to drugs of abuse was not due to increased inhibitory control of these neurons. Instead, it was due to excessive excitation of these neurons that prevented the generation of impulse activity. This phenomenon is termed depolarization inactivation and also is responsible for a lack of neuronal activity in certain brain areas at the later stages of seizure activity.
- The reduction in the electrical activity in dopamine neurons by excessive excitation qualitatively alters the responses of

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behavior, negative affect during play, difficult child temperament, marital conflict, and hours spent in child care) translated to higher levels of aggression at 18 months of age than children from families with a low risk factor.

Study Participants

Participants in this study were 226 families with 12 month old infants (110 girls and 116 boys) who volunteered for an ongoing longitudinal study of parenting and infant development. Three groups were examined: 1) 102 nonalcoholic families, consisting of parents with no or few current alcohol problems; 2) 92 families with alcoholic fathers and non-alcoholic mothers; and 3) 32 families with alcoholic fathers and heavy drinking mothers.

The parents in the study were primarily White and 88 percent were married. The average age for mothers was 31 years and for fathers 33 years. The names and addresses of these families were obtained from New York State birth records for Erie County. Families were excluded if birth records showed problems that might be indicative of prenatal exposure to drugs or heavy alcohol use. Mothers who reported drinking moderate to heavy amounts of alcohol during pregnancy were excluded from the study in order to control for potential fetal alcohol effects.

Background

A family risk factor or cumulative risk score was created for each family when the child was 18 months of age. Risk factors included number of hours in child care per week, difficult infant temperament, parental depression, parental antisocial behavior, spousal aggression, and parental negative affect during play. Families with scores in the upper 25 percentile of each factor (reflecting a higher level of risk) were assigned a score of 1 for that factor. The family's risk factor or composite risk score was created by adding the number of risk factors within the family. Thus, cumulative family risk score ranged from zero to twelve with higher scores indicating higher family risk.

Results and Discussion

- Parental alcohol abuse as a predictor. For the sample as a whole, aggressive behavior increased from 18 to 36 months, peaked at 36 months, and declined from 36 to 48 months. However, children with two alcoholic parents showed less decline in aggression from 36 to 48 months compared to children in the nonalcoholic group. Further, children with nonalcoholic parents had the lowest levels of aggressive behavior at all time points.
- Cumulative family risk as a predictor. Researchers expected that changes in aggression would be different for families with different risk levels. When cumulative family risk was examined, parental alcohol use was no longer a significant predictor of aggression. However, children with high family risk scores had higher initial levels of aggression than children in low risk families.
- Child gender. Boys with higher levels of family risk had higher 18 month aggressive behavior than boys with lower levels of family risk. Boys with two alcoholic parents had significantly less of a decline in aggression from 36 to 48 months compared to boys in the nonalcoholic group.

  For girls, higher levels of family risk were also related to higher levels of aggressive behavior at 18 months. Girls with higher levels of aggressive behavior at 18 months had a lower rate of decline in aggressive behavior over time.

As a whole, the children followed normal aggressive behavior patterns with aggressive behavior increasing until age three and then decreasing from three to four years of age. This trend is typical from toddler to preschool age among low-risk samples. However, children with alcoholic parents demonstrated deviations from this trend by exhibiting higher levels of aggression at all time points. Those with two alcoholic parents did not exhibit the normal declines. This was especially relevant for boys with two alcoholic parents. Consistent with previous research, it appeared that boys may be particularly vulnerable to the effects of parental alcoholism.

The results suggest that one important time for an intervention with these families may be the time between toddler to preschool age. Timing interventions to this age range may facilitate the decline in children's aggression between three to four years of age. It is possible that the boys of alcoholic parents in the study failed to develop the self-regulatory abilities expected of preschoolers. Therefore, targeting boys of alcoholic parents may be particularly important as boys show higher levels of aggression compared to girls. One intervention strategy may be to promote the development of self-regulatory or self-control skills at this age.

Limitations

- Reliance on self-report measures is a possible limitation. However, the average of both maternal and paternal reports was used in this study. Additionally, parental reports of childhood behaviors were found to be valid in other studies.
- It should also be noted that the sample was comprised of predominately White, educated, two-parent, dual earner families and so can only be generalized to this population.
- Given the nature of the study's design, the role of maternal alcohol problems could not be examined independently from paternal alcohol problems. However, in the majority of alcoholic families, maternal alcohol problems exist in the context of paternal alcohol problems and may be difficult to examine independently.

This study emphasized the importance of focusing on multiple predictors of child risk in alcoholic families and highlights the toddler to preschool period as an important period for intervention. Future studies are needed to explore what child and

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these neurons to incoming signals from other brain areas. Opposite to what was observed in animals without prior history of drug exposure, inhibitory signals from other brain areas now led to a dramatic increase in the activity of dopamine neurons. This effect was presumably achieved by removing the excessive excitation and therefore allowing dopamine neurons to resume impulse activity.

Background

Dopamine neurons located in the midbrain are the origin of the reward pathway in the brain. The activity of dopamine neurons is constantly modulated by incoming signals from other brain areas, especially those related to reward. It is believed both the basal level of dopamine neuron activity and changes in dopamine neuron activity regulated by incoming signals play important roles in the motivation and attention processes necessary to seek reward related stimuli.

Initial exposure to drugs of abuse causes these neurons to release dopamine in target areas, leading to a rewarding or "feeling good" experience and learning of reward signals. However, repeated use of drugs of abuse has been shown to cause long-lasting adaptive changes within the reward pathway. These adaptative changes, especially those in dopamine neuron cell body areas, play a critical role in drug craving and compulsive drug-seeking behaviors (Stewart, 2003).

Currently, there are very few studies investigating the long-term cellular changes in dopamine neuron cell body areas after repeated use of drugs of abuse. Most previous studies have examined changes in dopamine neurons shortly after (within a week) the termination of drug exposure. Utilizing the *in vivo,* single-unit recording method, Dr. Shen's laboratory studied the electrical activity (impulses) of individual dopamine neurons that tightly control the synthesis and release of dopamine in the target areas. They also included different classes of drugs of abuse for the study. The goal was to investigate if potential changes in dopamine neurons indeed represent a "common" adaptation of drugs of abuse.

Discussion of Findings

The results of the present study show that repeated exposure to different types of drugs of abuse such as stimulants or alcohol leads to a persistent reduction in the electrical activity of dopamine neurons that is observable long (three to six weeks) after the termination of repeated drug exposure. In addition, observations from this study suggest that reduced activity of dopamine neurons appears to be a result of excessive excitation, leading to cessation of neuronal impulses. A previous study from Dr. Shen's laboratory (Shen and Choong, 2006) suggests that this effect could be a result of a time-dependent escalation in the excitation of DA neurons that begins right after the termination of repeated drug use.

Dr. Shen's current study suggests the reduced activity in dopamine neurons could be an important neural substrate for addiction for the following reasons. First, it depicts a common and persistent neural adaptation within the reward pathway after repeated use of different types of drugs of abuse. Second, the long-lasting nature and the time-dependent development of this effect correlate well with the persistent nature and time-dependent intensification of addicted behavior during abstinence.

The results from the current study show that long after the termination of repeated exposure to drugs of abuse, not only is the basal level of dopamine neuron activity reduced, but the regulation of dopamine neurons by incoming signals is altered. For example, results from this study show that activation of the nucleus accumbens, a brain area within the reward pathway responsible for the execution of addiction related behavior, slightly suppresses dopamine neuron activity in rats without a history of drug exposure. However, in animals repeatedly exposed to drugs of abuse, the same accumbens activation dramatically increased dopamine neuron activity. This effect was probably achieved by increased inhibitory tone from nucleus accumbens stimulation which facilitated the removal of excessive excitation.

In a previous study, Dr. Shen's laboratory demonstrated that an acute stimulant administered in a low dose (which in control animals slightly decreases dopamine neuron activity) can also dramatically increase the activity in these neurons in repeated ethanol treated animals (Shen, 2003). The current study results suggest that the responses of dopamine neurons to incoming signals and acute drugs of abuse are qualitatively altered in animals with a prior history of drug exposure. Given the importance of the reward pathway in mediating reward or the "feel good" experience, these results suggest that external and internal stimuli that do not lead to particular reward or positive feeling in individuals with no drug history would instead, in individuals with a drug history, carry a strong reward or positive feeling and therefore be more likely to initiate a behavioral response for approaching these stimuli. This process could explain drug craving and drug seeking behavior.

Taken together, the persistent reduction in dopamine neuron electrical activity due to excessive excitation following repeated exposure to drugs of abuse represents a potentially new and critical neural mechanism for addiction. Importantly, these new findings provide a working model that predicts a novel set of hypotheses regarding the nature of the change in the reward pathway consequent to drug-related cues and acute drug exposure in individuals with and without a prior drug abuse history.

Future Studies

The most important work in the future will be to verify the direct link between reduced electrical activity in dopamine neurons by excessive excitation, and addicted behaviors after

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The Development of Aggression (cont'd)

family factors serve to exacerbate or maintain child aggression in the preschool years and what factors serve to protect against child aggression.

This study was made possible by grants from the National Institute on Alcohol Abuse and Alcoholism (1RO1-AA10042) and the National Institute on Drug Abuse (1K21-DA00231).

Long-term Reduction (cont'd)

repeated exposure to drugs of abuse. To that end, Dr. Shen plans to incorporate behavioral models of addiction in her studies. If a direct link is confirmed, she will investigate the cellular mechanism underlying the persistent changes in dopamine neurons. She also will examine whether long-term normalization of dopamine neuron activity can be achieved with certain pharmacological agents and whether such normalization leads to amelioration of addiction. Dr. Shen plans to conduct these future studies in collaboration with other RIA scientists who have expertise in behavioral models of addiction and cellular electrophysiology, including Drs. Samir Haj-Dahmane, Jerry B. Richards, and Alexis C. Thompson.

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This research was supported by National Institutes of Health (NIH) Grant AA12435.

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