

**Embargoed until Nov. 10, 3:30 p.m. PST**  
Press Room, Nov. 9–13: (619) 525-6260

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**NEW EVIDENCE ON THE BIOLOGICAL BASIS OF HIGHLY IMPULSIVE AND  
AGGRESSIVE BEHAVIORS**

*For want of a receptor: some behaviors shaped during early development*

**SAN DIEGO** — Physical and chemical changes in the brain during development can potentially play a role in some delinquent and deviant behaviors, according to research released today. Studies looking at the underlying mechanisms that influence our ability to exercise self-control were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Understanding the impact of changes in specific prefrontal regions during brain development could lead to new treatments and earlier interventions for disorders in which impulsivity plays a key factor. The research may have implications for understanding and dealing with aggressive and troublesome behaviors.

Today's new findings show that:

- The absence of serotonin receptors during early development leads to highly aggressive and impulsive behaviors in mice. Impulsivity, but not aggression, returns to normal levels by reintroducing the receptors (Katherine Nautiyal, PhD, abstract 754.07, see attached summary).
- Adolescents react more impulsively to danger than adults or children, and the prefrontal cortex works harder to exert control over impulsive responses to threatening cues (Kristina Caudle, PhD, abstract 852.14, see attached summary).

Other recent findings discussed show that:

- Weak control of the brain's prefrontal cortex (which monitors personality, decision-making, and self-restraint) over regions associated with reward and motivation could explain the lack of self-control experienced by anti-social individuals (Joshua Buckholtz, PhD, presentation 194.01, see attached speaker summary).
- Criminal defendants increasingly use brain science to explain their actions, pointing to brain scans and the scientific literature for evidence that brain impairments affect behavior. This is impacting how the legal system assigns responsibility and punishment for criminal wrongdoing in the United States (Nita Farahany, JD, PhD, presentation 301, see attached speaker summary).

“Our deeper understanding of the origins of delinquent behavior can be a double-edged sword,” said press conference moderator BJ Casey, PhD, of Weill Cornell Medical College, an expert in attention, behavior, and related brain disorders. “While we're making tremendous gains in neuroscience that should lead to improved treatments, our biological insights also have implications for criminal cases and the judicial process that we need to understand.”

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. More information about behavior and the brain can be found at [BrainFacts.org](http://BrainFacts.org).

Related Neuroscience 2013 Presentations:

Albert and Ellen Grass Lecture: **The Neural Circuitry of Sex and Violence**  
Monday, Nov. 11, 3:30—4:40 p.m., Ballroom 20

Symposium: **Law and Neuroscience**  
Wednesday, Nov. 13, 8:30—11 a.m., Room 6A

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## Abstract 754.07 Summary

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### **Capacity For “Serene” Behavior Programmed During Early Development In Mice** *Absence of a key brain receptor during development linked to aggression and impulsivity in adults*

Blocking serotonin receptors during development results in highly aggressive and impulsive behavior, according to new animal research. Reintroducing the receptors in adulthood suppresses impulsivity, but not aggression, to normal levels. These findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world’s largest source of emerging news about brain science and health.

Previous studies have identified a link between low serotonin levels and impulsive, violent aggression. However, therapeutic treatments that used antidepressants to increase serotonin generally did not reduce the negative behaviors. The new research, led by Katherine Nautiyal, PhD, from Columbia University, identified a specific serotonin receptor (5-HT1B) as a key factor in aggressive and impulsive behaviors. Mice lacking this receptor during development exhibited more frequent and intense fighting than did control mice. They were also more impulsive in neutral situations, more vulnerable to abusing drugs, and demonstrated less restraint, even when rewarded to do so.

“Violence is a pervasive societal problem with few effective treatments available, and violence and impulsivity often go hand-in-hand,” said Nautiyal. “Our research illuminates a new path for the development of medicines to treat disorders in which impulsivity is a key factor — including pathological gambling, suicide, and drug addiction.”

Research further revealed that a lack of 5-HT1B during the early postnatal developmental period leads to aggressive and impulsive behavior. Interestingly, the impulsivity but not the aggression could be suppressed when the receptor levels were returned to normal in adult mice. This suggests that 5-HT1B expression during development is required for the formation of brain circuits that promote non-aggressive, more serene, behavior.

Research was supported with funds from National Institute of Mental Health and National Center for Responsible Gaming.

Scientific Presentation: Wednesday, Nov. 13, 10–11 a.m., Halls B-H.

754.07. A lack of serotonin 1B receptors during development results in aggressive and impulsive behavior

**K. M. NAUTIYAL<sup>1</sup>**, K. F. TANAKA<sup>2</sup>, C. BLANCO<sup>3</sup>, R. HEN<sup>1</sup>, S. E. AHMARI<sup>3</sup>; <sup>1</sup>Neurosci., Columbia Univ., NEW YORK, NY; <sup>2</sup>Div. of Neurobio. and Bioinformatics, Natl. Inst. for Physiological Sci., Okazaki, Japan; <sup>3</sup>Psychiatry, Columbia Univ. / New York State Psychiatric Inst., NEW YORK, NY

**TECHNICAL ABSTRACT:** The serotonin 1B receptor (5-HT1B R) has been implicated in the modulation of aggressive and impulsive behavior. However, neither the localization nor the sensitive period of these effects has been identified. Given the broad localization of the receptor throughout the brain and evidence of serotonergic modulation of brain development, an inducible and tissue specific knock-out is necessary to delineate the role of 5-HT1B R in aggression and impulsivity. We have therefore generated a mouse model that permits temporal and spatial regulation of 5-HT1B R. A novel transgenic mouse was created by inserting a tetracycline operator (tetO) between the promoter and coding region of the 5-HT1B R (tetO1B), which did not affect baseline receptor expression in the brain. Crossing tetO1B mice to mouse lines expressing the tetracycline-dependent transcriptional silencer (tTS) transgene under the control of various promoters allows for tissue specific knock-down of 5-HT1B R, which can be rescued by treatment with doxycycline (DOX). Using the ubiquitous  $\beta$ -Actin promoter to drive tTS expression,  $\beta$ -Actin-tTS/tetO1B mice had complete elimination of brain 5-HT1B Rs. This resulted in increased behavioral impulsivity as measured in the differential reinforcement of low-rate responding (DRL) operant conditioning paradigm, which rewards the ability to inhibit responding.  $\beta$ -Actin-tTS/tetO1B mice were also highly aggressive compared to littermate controls as measured in assays of male territorial and female peripartum aggression. Interestingly, full rescue of 5-HT1B R expression in adulthood with DOX did not ameliorate the aggressive phenotype. This suggests that developmental expression of 5-HT1B R is important for the maturation of the neural circuits underlying aggressive behavior. To localize the receptors involved in aggressive behavior, tTS was placed under the control of Pet-1 or CaMKII promoters to target autoreceptor and heteroreceptor populations, respectively. Pet-tTS/tetO1B mice lack 5-HT1B autoreceptors located on serotonergic cells, and displayed low levels of aggression not significantly different from their littermate controls. In contrast, CaMKII-tTS mice that lack cortical, striatal and hippocampal 5-HT1B heteroreceptors (on non-serotonergic cells), displayed increased aggressive behavior. This suggests that receptors in cortex, striatum, and/or hippocampus modulate aggressive behavior. Current research is aimed at identifying the specific receptor population(s) that play a role in aggressive and impulsive behavior, as well as determining the sensitive period during which they have their effects.

## Abstract 852.14 Summary

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### **Teen Brains Show Unique Response To Danger**

*Impulsivity in the face of risk may drive increased criminal behavior during adolescence*

New findings show that adolescents react more impulsively to threats than either adults or children — and have to work harder to suppress this impulse. The study results may help explain why adolescents engage in criminal activity more than either children or adults. The findings were presented at Neuroscience 2013, the annual meeting of the Society for Neuroscience and the world’s largest source of emerging news about brain science and health.

“Crimes are often committed in emotionally charged or threatening situations, which push all the wrong buttons for reasoned decision-making in the adolescent brain,” said lead author Kristina Caudle, from Weill Cornell Medical College. “It’s fascinating because, although the brains of young children are even less mature, children don’t exhibit the same attraction to risky or criminal behaviors as do adolescents.”

The basis for increased criminal activity during adolescence has remained largely unknown. The new research shows that threatening situations provoke more impulsive responses in adolescents than in children or adults, and requires greater activity in the ventromedial prefrontal cortex (vmPFC) to exercise self-restraint. The prefrontal cortex is the front part of the brain responsible for monitoring personality and impulse control.

To assess this, researchers presented 83 individuals between the ages of 6 and 29 years with neutral or threatening facial expressions while undergoing functional magnetic resonance imaging (fMRI). Participants were asked to press a button when presented with the neutral faces and to refrain from doing so when presented with threatening faces. Teens were less able to refrain from pressing the button when confronted by the threatening facial expression than either the children or adults.

The adolescents who were successful at controlling their response to the threat cue showed significantly greater activity in the vmPFC than did younger or older participants. In adults, the vmPFC helps regulate responses to emotional situations. But in adolescents, this brain area is in a state of change. “Our research suggests that biological changes of the vmPFC during adolescence influence emotional processes, such that dangerous activities bring their own emotional reward,” Caudle said.

Research was supported with funds from the National Institutes of Health (National Institute on Drug Abuse, National Institute of Mental Health, and National Institute of Child Health and Human Development) and the MacArthur Foundation.

Scientific Presentation: Wednesday, Nov. 13, 2–3 p.m., Halls B-H.

852.14, Drawn to Danger: Teens approach rather than retreat from threat

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**TECHNICAL ABSTRACT:** There is a significant inflection in criminal activity during adolescence, but the basis for this increase remains largely unknown. Poor decision making and increased risk taking have been suggested to explain these behaviors. Yet adolescents are better in their reasoning and decisions than children and show less risk taking than adults when outcomes are known. Much less consideration has been given to the role of changes in emotional processes during adolescence, although many juvenile offenses occur in emotional situations. The current study uses a measure of impulsivity in combination with cues that signal threat to assess developmental changes in these processes. Eighty-three participants between the ages of 6 and 29 years were scanned using functional magnetic resonance imaging (fMRI) while completing a go-no/go task, using threat and neutral facial expressions as target (go) and non-target (no-go) stimuli. The results show that teens impulsively react to threat cues more than adults or children and show greater activity in ventromedial prefrontal cortex when successfully suppressing these impulses. This region has been implicated in emotion regulation (i.e., choosing adaptive responses to emotional cues in a given situation). These findings suggest that maturational changes in ventromedial prefrontal circuitry during adolescence may increase the likelihood of approaching, rather than withdrawing, from danger.

**Speaker Summary (194.01)**

**Speaker: Joshua Buckholtz, PhD**  
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**Parsing Self-Control In Incarcerated Criminals: Impulsive-Antisocial Behavior Tracks Variability in Corticostriatal Circuit Structure**

Sunday, Nov. 10, 8–9 a.m., Halls B-H

Poor self-control is a core feature of criminal antisocial behavior, however, it is poorly understood. Using a mobile fMRI scanner, we obtained detailed measurements of brain structure in a sample of incarcerated male offenders. We found that, in general, individuals with more severe impulse control problems had a larger volume of gray matter in regions linked to reward and motivation. However, while poor impulse control was linked to lower prefrontal cortex volume in non-psychopathic offenders, psychopaths with impulse control deficits showed evidence of preserved brain structure in this region.

Our previous brain imaging research has demonstrated that impulsive and antisocial individuals release more of the neurotransmitter dopamine in brain regions linked to reward and motivation, such as the ventral striatum. They also show higher activity levels in the striatum when given the opportunity to win money. Based on these findings, we have suggested previously that the brains of people predisposed to antisocial behavior “over-react” when faced with the chance to get rewards (e.g. money, sex, drugs, or status). This “reward hypersensitivity” and resulting high reward drive may lead to some of the impulse control deficits that are typical of criminal offenders. This idea is supported by other work showing that incarcerated criminal psychopaths have structural abnormalities in brain reward regions.

In a sample of 49 male prisoners who received a comprehensive clinical and diagnostic evaluation, we used two approaches to measuring brain structure via MRI. Both types of analyses revealed that offenders with the most severe self-control deficits had relatively thinner cortex in prefrontal regions linked to attention, planning, and inhibition, along with a larger volume of gray matter in the striatum. Strikingly, when we separated these offenders according to psychopathy diagnosis, the “thinner” prefrontal cortices were only observed in the non-psychopathic offenders. In other words, high-impulsive psychopaths and non-psychopaths share brain structure differences in reward regions, but the psychopaths appear to have relatively preserved brain structure in the prefrontal cortex. All of these findings remained evident even after controlling for other potential confounds, such as participant age or substance abuse history.

These findings support our hypothesis that self-control deficits in antisocial individuals could be driven by weak prefrontal control over striatum-driven reward responses. They also provide a biological validation of and mechanism for the important clinical distinction between high-impulsive psychopathic and high-impulsive non-psychopathic individuals.

This work was supported by the Alfred P. Sloan Foundation.

## Speaker Summary (301)

**Speaker: Nita Farahany, JD, PhD**  
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David Kopf Lecture on Neuroethics: **Blaming the Brain: Behavioral Sciences in the Courtroom**  
Monday, Nov. 11, 10–11:10 a.m., Ballroom 20

Criminal defendants increasingly use brain science to explain their actions, pointing to brain scans and the scientific literature for evidence that brain impairments affect behavior. This practice is influencing the outcomes of criminal cases to a growing degree.

Although scientists caution against the use of early research linking neurological differences to human behavior, their advice has gone unheeded. Even the gravest decisions in criminal law, including imposition of a death sentence on a criminal defendant, already hinges on evidence stemming from scientific results from behavioral genetics and neuroscience research.

Defense attorneys have relied upon behavioral genetics and neuroscience research when seeking to exculpate criminal defendants, to bolster pre-existing legal defenses, or to mitigate the culpability and punishment of their clients. Prosecutors have seized upon the double-edged potential biological predisposition evidence by seeking to denigrate defendants' characters or underscore their likely future dangerousness.

As the science continues to develop, its potential use in criminal investigations, interrogations, and predictions of dangerousness will inevitably expand. The discovery of more specific biological and neurological contributions to violence, aggressiveness, impulsivity, substance abuse, even though highly contestable and indeterminate as a scientific matter, has foreshadowed an inevitable re-examination of the U. S. criminal justice system.

Indeed, the United States Supreme Court has already become involved in evaluating the relevance of neurological development to criminal culpability in a series of cases addressing the constitutionality of death sentences and life without the possibility of parole for juveniles. Liberty, justice, privacy, and the structure and purpose of the U. S. criminal justice system are all at issue.

Scholars and commentators had assumed that neurological evidence was used only in the punishment phase of death penalty cases, but early research into the issue suggested its use might be far more prevalent and impactful in criminal cases than assumed. To test the hypothesis that criminal defendants are increasingly introducing neurological evidence in criminal cases and that such evidence was having a broader impact than assumed on criminal case outcomes, I undertook a systematic study on the use, prevalence, and impact of such evidence in U.S. criminal cases.

In this research, over 1,500 judicial opinions were identified that discussed the use of neuroscience introduced by a criminal defendant in a criminal case. Using a detailed set of coding instructions, and a team of over 20 law students and undergraduate students, 78 variables were coded in each case, including the nature of the criminal offense committed, the admissibility of the evidence presented, the composition of the judicial panel, the nature of the legal claim addressed by the neurological information and more.

The results demonstrate a year over year increase in judicial opinions discussing the use of neurological evidence by a criminal defendant in both violent and non-violent criminal cases. Criminal defendants are mounting more and more sophisticated defenses bolstered by neurological evidence to claim that their brain — and not their voluntary and conscious deliberation — helps to explain their criminal conduct.

Criminal defendants have found some success with such claims, particularly in challenging their competency to stand trial, the severity of their punishment, and the degree of deliberation they should be held accountable for. Some

defendants have even had their death sentences vacated based on new neurological evidence they have presented, while others have successfully argued that they received ineffective assistance of counsel when their attorney failed to have them evaluated for neurological impairments.

At the same time, over the eight-year period studied judges have spilled far more ink on the neurological evidence introduced in recent years than in prior ones, and the discussion of neuroscience in criminal cases has become far more sophisticated. Far from being used as a last-ditch attempt in death penalty cases, these results show that the use of neuroscience in criminal law is having transformative effects on how we assign responsibility and punishment for criminal wrongdoing in the United States.