Embargoed until Nov. 13, 10 a.m. PST
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Studies Pinpoint Circuits, Hormones, and Brain Regions Involved in Social Behavior

Findings reveal potential new targets for treating autism spectrum disorder, schizophrenia, and anxiety

SAN DIEGO — In all animals, neural mechanisms underpin emotion and social interactions. Understanding how these mechanisms influence social behavior may provide new treatment strategies for autism spectrum disorder, schizophrenia, and anxiety disorders, according to research presented today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Autism spectrum disorder affects 1 in 65 children in the United States, and one of the most recognizable symptoms is reduced social interaction, something also observed in some anxiety disorders. Additionally, autism and schizophrenia both disrupt the ability to detect and respond to the emotions of others — such as offering comfort to a distressed peer.

Today's new findings show that:

- The levels of a receptor implicated in social bonding predicts how likely prairie voles are to console each other in times of stress, a discovery that may help explain behaviors observed in autism and schizophrenia (James Burkett, abstract 387.03, see attached summary).
- A hormone involved in social bonding and a neurotransmitter involved in reward work together to promote social interaction in mice, suggesting that manipulating this system may be important for treating social impairments seen in autism (Lin Hung, abstract 387.02, see attached summary).
- The comfort people feel when surrounded by others may be due to activation of part of the prefrontal cortex, providing a potential target for treatments aimed at reducing fear and anxiety (Zoe Donaldson, abstract 634.22, see attached summary).
- Infants' brains respond differently to different emotions, with fearful faces inducing the most widespread network activity from as young as 5 months old (Catherine Stamoulis, abstract 678.09, see attached summary).
- A tendency to dread social situations may be explained by structural differences in brain regions that regulate emotion, attention, and perception, a finding that could help in developing therapies for social anxiety (Bonni Crawford, abstract 268.06, see attached summary).

"Today's findings broaden our understanding of the social brain," said press conference moderator Steve Fleming, PhD, of University College London, an expert in self-awareness and metacognition. "By understanding the processes behind our interactions with and reactions to others, we can create better interventions for when those processes go awry."

The research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about the neurobiology of social behavior at *BrainFacts.org*.

Related Neuroscience 2016 Presentation

Special Lecture: The Social Brain in Human Adolescence
Wednesday, Nov. 16, 11:30 a.m.-12:40 p.m., SDCC Ballroom 20

Abstract 387.03 Summary

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Oxytocin Receptor Levels Predict Comforting Behaviors in Prairie Voles

Finding has implications for behaviors observed in autism spectrum disorder, schizophrenia

Different levels of a receptor for a hormone involved in social bonding may explain individual variation in offering comfort during stressful situations, according to new animal research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Like humans, animals console each other in times of distress: Monkeys hug and kiss, and prairie voles groom each other. Previous research indicates oxytocin — a hormone that promotes social and maternal bonding — acts in the anterior cingulate cortex (ACC) of the prairie vole brain to encourage consoling behavior. In humans, the ACC activates when people see others in pain.

Some degree of personal distress motivates comforting behaviors, but too much actually makes animals (including humans, chimpanzees, and rats) less likely to offer comfort. In this study in prairie voles, researchers explored whether the amount of the receptor for oxytocin correlates with empathetic behaviors, and they predicted the animals with the greatest number of oxytocin receptors would experience too much personal stress and comfort others less.

Researchers exposed prairie voles to light foot shocks while "observer" animals watched. Afterward, they monitored the number of consoling behaviors like grooming that the observer prairie voles performed and measured the amount of oxytocin receptor in the animal's ACC. As predicted, prairie voles with the highest levels of oxytocin receptor displayed the fewest consoling behaviors.

"This finding suggests that an individual's tendency to show pro-social consolation can be predicted by measurable characteristics in the brain," said lead author James Burkett, PhD, of Emory University. "It has important implications for understanding and treating psychiatric disorders in which detecting and responding to the emotions of others can be disrupted, including autism spectrum disorder and schizophrenia."

Research was supported with funds from the National Institutes of Health and Emory University.

Scientific Presentation: Monday, Nov. 14, 1:30-1:45 p.m., SDCC 5B

Abstract 12502, Consolation behavior in prairie vole is predicted by oxytocin receptor density in anterior cingulate cortex
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TECHNICAL ABSTRACT: Empathy for the pain and suffering of others is a widespread mechanism among social animals that provides a motivation for prosocial behaviors. Consolation is one such prosocial response that has been observed in a wide range of animals, including a laboratory rodent, the prairie vole (*Microtus ochrogaster*). Our previous research demonstrated that consolation behavior in the prairie vole is empathy-based and is regulated by oxytocin receptor (OTR) signaling in the anterior cingulate cortex (ACC). OTR density in the ACC varies between individual prairie voles, yet the role of this biological variation in contributing to behavioral variation is unknown. We examined the relationship between OTR density and consoling behavior using data from five experiments, split into a discovery sample (Expt. 1, N=54) and a replication sample (Expt. 2, N=7; Expt. 3, N=12; Expt. 4, N=12; Expt. 5, N=43). Analysis of both samples revealed a negative correlation between consoling response and OTR density in the ACC ($p=0.02$, $r=-0.3$, Hedges' $g=-0.6$) but not OTR density in other brain regions. Voles in both the highest and lowest quartiles of OTR density showed a significant consoling response (high, $p=0.003$; low, $p=0.0002$), but voles in the lowest quartile performed more consoling behavior than those in the highest quartile ($p=0.03$). These results show that the magnitude of the consoling response in individual animals can be predicted by the density of OTR in the ACC, suggesting that OTR density in this region may be behaviorally relevant. High OTR density in ACC may drive an increase in personal distress in response to the distress of others, which is related to lower levels of helping in humans, great apes and rats.

Abstract 387.02 Summary

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Oxytocin May Promote Social Interaction in Mice by Influencing Dopamine Activity

Results suggest potential for oxytocin therapy in treating autism spectrum disorder

The desire to be social may hinge on the interplay between a hormone that promotes bonding and a neurotransmitter that triggers feelings of reward, according to new animal research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. The findings could have implications for the treatment of autism spectrum disorder, which can involve varying degrees of social impairments.

The inability to experience pleasure from social interactions may underpin some of the social problems characteristic of autism. Previous research has tried to use oxytocin, a hormone that increases social bonding, as a potential therapy for autism, but the results have been mixed and it's unclear how oxytocin may exert its effects. One theory posits that oxytocin influences the activity of neurons that release dopamine, a neurotransmitter involved in motivation and reward

In this study of mice, researchers manipulated and measured oxytocin signaling in the ventral tegmental area (VTA), the home of dopamine neurons. When they disrupted oxytocin signaling to dopamine neurons, mice were less likely to choose to interact with other mice. In a separate experiment, researchers found oxytocin neurons became active during social interactions. What's more, the team enhanced the animals' social interactions by directly activating the oxytocin neurons. Mice receiving direct activation of these neurons behaved as if it were a reward: They preferred to stay on the side of an arena in which they received the stimulation, an effect that was even stronger when the stimulation was paired with a social context. The results indicate oxytocin's effects on pleasure-seeking and social interaction may arise in part from its ability to enhance activity of dopamine neurons in the VTA.

"Our research suggests that oxytocin is able to increase social interaction via its ability to enhance the motivational value of such interactions," said lead author Lin Hung of Stanford University. "This study gives us an indication that oxytocin therapy can be most effective when treatment is paired with social context."

Research was supported with funds from the Simons Foundation Autism Research Initiative and the Australian National Health and Medical Research Council.

Scientific Presentation: Monday, Nov. 14, 1:15-1:30 p.m., SDCC 5B

Abstract 5583, Oxytocin gates VTA dopamine neurons to promote pro-social behaviors
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TECHNICAL ABSTRACT: Oxytocin (OT) is often considered a pro-social hormone yet the mechanisms by which it promotes sociability are unclear. One hypothesis posits that oxytocin affects mesolimbic reward circuitry to increase motivation for pro-social behavior. Previous studies have shown that OT increases social drive at least in part via its effect in the nucleus accumbens (NAc). However, the critical role of the ventral tegmental area (VTA) in motivated behaviors and the presence of OT receptors and fibers in the VTA suggest that OT's effects on VTA dopamine (DA) neurons may also contribute to the gating of social behavior. To determine the necessity of OT signaling in the VTA and its relevance for social motivation, we ablated or reduced oxytocin signaling in VTA DA neurons via a number of different strategies. Silencing of paraventricular nucleus (PVN) hypothalamic neurons projecting to the VTA lead to a reduction in social reward as measured by a social conditioned place preference assay. In addition, knocking out OT receptors in the VTA by injection of a Cre virus into the VTA of conditional OT receptor knockout mice as well as from DA neurons by crossing these mice with DAT-Cre mice both reduced social reward. If OT release in VTA and NAc are important for gating social behavior, social interactions should cause OT release in these structures via increases in the activity of OT neurons. Using *in vivo* calcium imaging, we found that novel social interactions increases the activity of PVN OT neurons. To determine the consequences of direct activation of these neurons, we expressed a variation of channelrhodopsin (ChETA) in PVN OT neurons and found that their optogenetic activation was sufficient to elicit conditioned place preference and enhance social interaction. Social reinforcement was also observed during PVN OT neuron terminal stimulation in the VTA; an effect that was blocked by an OT receptor antagonist. To determine mechanistically how OT is affecting VTA DA neurons, we made whole cell patch clamp recordings from a homogeneous population of VTA DA neurons that project to the NAc medial shell (NAcMedS). Application of the OT receptor agonist TGOT on average reduced evoked IPSCs while at the same time modestly enhancing evoked EPSCs, resulting in a net increase in excitation onto these neurons. Together these results demonstrate that the action of OT on VTA DA neurons is necessary and sufficient for enhancing the motivation for social interactions.

Abstract 634.22 Summary

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Scientists Identify Brain Region Involved in Peer-Provided Comfort in Mice

Activating neurons in the area reduced animals' fear in threatening situations

New animal research implicates a region of the brain in the comfort we get from being around others during difficult times, as described in a study presented today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. Targeting the area may help reduce fear and anxiety following trauma.

Social relationships — with parents, children, romantic partners, or friends — are important aspects of people's daily lives and affect mood and behavior. Having others around during times of trauma can help people cope; this "social buffering" decreases the risk of mental illness and helps speed recovery from heart attacks and cancer. This is true for other species as well, such as goats and monkeys.

In this study, researchers explored the neural processes behind social buffering by placing mice in environments that elicit fear, such as cages in which they had previously received an electric shock. When accompanied by a familiar mouse, the animals froze less — a sign of reduced fear — compared with entering the environment alone. The team identified a set of neurons in the prefrontal cortex that activated when mice interacted with a familiar mouse, but not an unfamiliar mouse or novel object. Activating these neurons in the mice decreased freezing in threatening environments.

"Our findings suggest that when two animals interact and these cells are activated, it may lead to social buffering," said senior author Zoe Donaldson, PhD, of the University of Colorado, Boulder. "The long-term goal of this work is to identify the brain circuits that mediate the positive effects of such interactions. From this we may be able to harness the natural mechanisms that alleviate stress and anxiety to develop new treatments."

Research was supported with funds from the American Foundation for Suicide Prevention, the National Institute of Mental Health, and the Hope for Depression Research Foundation.

Scientific Presentation: Tuesday, Nov. 15, 2-3 p.m., Halls B-H

Abstract 13316, Social modulation of conditioned and innate fear responses
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TECHNICAL ABSTRACT: Amongst social animals, the presence of a conspecific companion can have powerful effects on mood and behavior. In particular, the social modulation of fear and anxiety represents a highly conserved trait, as both humans and rodents display decreases in anxiety and stress responses when an affiliative conspecific is present. However, the neural processes underlying this social buffering phenomenon remain largely unknown. Our group has found that in mice, conspecific presence decreases freezing in both conditioned and innate fearful contexts. In order to identify neural populations that may contribute to social buffering of fear responses, we used a mouse line in which *Arc*-expressing neurons are indelibly labeled following interaction with a novel conspecific. We identified a subset of cells within the infralimbic prefrontal cortex (ILPFC) of male and female ArcCreER^{T2} mice that are labeled in response to interacting with a novel, ovariectomized female conspecific but not in response to a toy mouse, novel object, or food reward. Optogenetic activation of conspecific-labeled ChR2-eYFP^{+} neurons decreases freezing in contextual and innate fearful contexts, without impacting locomotion or eliciting reward, recapitulating the effects of conspecific presence. Together, these studies suggest that activation of neurons associated with an affiliative conspecific in the ILPFC may be sufficient to mediate the effects of conspecific presence on fear responses. Thus, targeting this cell population may provide novel therapeutic opportunities that harness circuits naturally engaged by social interaction in order to treat fear and anxiety-related disorders.

Abstract 678.09 Summary

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Emotional Faces Activate Distinct Networks in Infants' Brains

Networks appear to remodel during early life to increase efficiency

Brain networks associated with processing facial expressions come on line early in life and vary based on the type of emotion, according to new research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The brain develops as interconnected networks working together to process and respond to outside information. But little is known about how these networks mature, particularly during the early years, when the brain undergoes massive structural and functional changes.

The researchers explored how brain networks involved in emotional face processing become connected, particularly in the first years of life, by analyzing electroencephalograms from a large cohort of typically developing infants at ages 5 months, 7 months, 12 months, and 36 months. They focused on neural responses to happy, angry, and fearful faces. At 36 months, the team also documented brain responses to neutral faces. No matter the age, fearful faces triggered more coordinated activity across networks, indicating mechanisms for recognizing fear may be in place soon after birth. At 36 months, neutral faces generated the least amount of coordinated activity between networks. Between 12 and 36 months, the number of network connections decreased, implying the brain is reorganizing and deleting unnecessary connections to increase efficiency.

"These findings suggest that differential network activation in response to fearful faces occurs as early as 5 months and persists consistently across the first three years of life, despite additional developmental changes in the overall organization of the brain," said lead author Catherine Stamoulis, PhD, of Harvard Medical School.

Research was supported with funds from the National Science Foundation Brain Initiative through its Cognitive Neuroscience Program and the National Institute of Mental Health

Scientific Presentation: Wednesday, Nov. 16, 8-9 a.m., Halls B-H

Abstract 9350, Dynamic changes in brain network activation during emotional face processing in the developing brain.
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TECHNICAL ABSTRACT: There is substantial evidence that adult brains are organized into parsimonious and optimally connected small-world and scale-free networks, which facilitate efficient processing of sensory information and cognitive performance. In contrast, little is known about the dynamic development of these networks in early life, their progressive optimization and neural computation across incompletely myelinated and redundantly connected circuits. Furthermore, there is limited systematic evidence that core networks, which are involved in cognitive function that is critical for survival, may develop at distinct rates from those involved in higher-level function. Using longitudinally acquired electrophysiological (EEG) data measured at <12 months and 36 months from 58 typically developing infants, this study investigated changes in the organization of distributed functional network activation in response to emotionally salient faces (happy, angry, fearful and neutral (only at 36 months)) during early development. A significant increase in network connectivity in response to fearful faces (compared to happy and angry faces) was estimated both at <12 months ($p<0.001$) and 36 months ($p<0.01$) across neural oscillations. This indicates that the mechanisms underlying network activation in response to fear may be in place at birth or the first few months of life. However, differential clustering in connectivity was also estimated in oscillation-specific networks, including higher connectivity in frontal areas in the gamma network and higher connectivity in parieto-occipital areas in the alpha network. A significant decrease in the number of network connections was estimated from <12 to 36 months across oscillations ($p<0.001$). Finally the lowest number of network connections was estimated in response to neutral faces ($p<0.0001$). These findings suggest that differential network activation in response to fearful faces occurs as early as 5 months and persists consistently during the first 3 years of life, although functional network topologies change dynamically during this period becoming increasingly sparse and clustered in a frequency-specific manner.

Abstract 268.06 Summary

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Differences in Brain Structures Help Explain Sociability

Areas involved in emotion, attention appear linked to people's expectations about social situations

The brains of people who find social situations distressing may differ from those who enjoy socializing, according to research released today at Neuroscience 2016, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Some people find social interactions pleasurable, while others dread them. These expectations, or "social expectancies," can impact mental and physical well-being, leading to increased anxiety or susceptibility to depression. While therapy may help with this distress and anxiety, researchers still don't understand how neurobiological processes, such as emotion, attention, and perception, contribute to these social expectancies.

In this study, researchers asked 100 healthy people to imagine a potential social event and rate their expectancies of it being enjoyable or distressing. The researchers then examined their brains with an MRI scan. The brains of people expecting social situations to be pleasurable contained a larger volume of gray matter— the part of the brain with neuronal cell bodies — in regions associated with the regulation of emotion, such as the ventromedial prefrontal cortex, than the brains of people with lower expectations of pleasure. On the other hand, the brains of people dreading social situations had greater gray matter volume in the amygdala, a region associated with social distress, and the right superior temporal sulcus, an area associated with social attention and perception. This suggests these people may be more attuned to signals of social threat and more mindful of them.

"Our results indicate that individual differences in social expectancy biases are most prominently reflected in the brain structure of key hub regions that implement emotion regulation and attention regulation," said lead author Bonni Crawford, PhD, of the Cardiff University Brain Research Imaging Centre. "This understanding may in time be of use in developing targeted interventions to alleviate the distress and societal costs caused by social disconnectedness."

Research was supported with funds from the United Kingdom's Economic and Social Research Council and Cardiff University's School of Psychology.

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

Abstract 2929, Brain structure and social belonging: expectations of social pleasure and pain are reflected in regional brain volumes
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TECHNICAL ABSTRACT: Human beings have a fundamental need to form and maintain social connections (a "need to belong"). Satisfaction of this leads to social pleasure, while failure to satisfy these needs results in social pain. Previous research has focused on the neural correlates of reactions to social rejection and acceptance. However, much of the pleasure and pain of social life occurs in *anticipation* of things that have yet to come. To measure individual differences in such anticipatory processes, we have developed a novel self-report measure, the levels of dispositional expectancies for social threat and reward scale (LODESTARS). The LODESTARS is a 10-item inventory examining the extent to which participants expect to experience social reward and social punishment during an imminent vividly imagined social encounter with previously unknown individuals. Data from 848 participants demonstrate that the LODESTARS has a clear two-factor structure and excellent psychometric properties. The brain-structural correlates of dispositional social threat and reward expectancies were examined using voxel-based morphometry (VBM). Regional grey matter volume (GMvol) of 100 healthy participants (mean age 24 years; 26 males) was assessed. High-contrast T1-weighted anatomical images were acquired using a 3-Tesla MRI scanner and analysed using SPM12. To correct for multiple comparisons across the whole brain, non-stationary cluster extent correction was implemented. Age, gender and total brain volumes were accounted for. Higher social threat expectancies were associated with greater GMvol in brain regions involved in social attention and perception, including the right superior temporal sulcus (pSTS). This may reflect attentional bias and hypervigilance directed towards potential social threat signals in the environment. Supporting this interpretation, pSTS GMvol correlated *positively* with amygdala GMvol in our sample (Pearson's $r = .23$; $p = .021$). Higher expectancies of social reward and lower expectancies of social threat were associated with greater GMvol in brain regions implicated in emotion regulation, particularly right ventromedial PFC (vmPFC). Previous findings suggest that this region may function as a hub that modulates negative affective responses (perceived fear and aversiveness) across a broad range of paradigms. Corroborating this, vmPFC GMvol was *negatively* correlated with amygdala GMvol in our sample (Pearson's $r = -.27$; $p = .008$). Our findings may have implications for understanding the consequences of social connection on brain structure, as well as brain structural dispositions to mood disorder risk, including social anxiety and social anhedonia.