

Embargoed until Nov. 12, 12:45 p.m. PST
Press Room, Nov. 9–13: (619) 525-6260

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NEW LINKS BETWEEN SOCIAL STATUS AND BRAIN ACTIVITY

*Social stability affects the production of new brain cells;
ability of brain to adapt is key to coping with hierarchies and stress*

SAN DIEGO — New studies released today reveal links between social status and specific brain structures and activity, particularly in the context of social stress. 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.

Using human and animal models, these studies may help explain why position in social hierarchies strongly influences decision-making, motivation, and altruism, as well as physical and mental health. Understanding social decision-making and social ladders may also aid strategies to enhance cooperation and could be applied to everyday situations from the classroom to the boardroom.

Today's new findings show that:

- Adult rats living in disrupted environments produce fewer new brain cells than rats in stable societies, supporting theories that unstable conditions impair mental health and cognition (Maya Opendak, abstract 85.11, see attached summary).
- People who have many friends have certain brain regions that are bigger and better connected than those with fewer friends. It's unknown whether their brains were predisposed to social engagement or whether larger social networks prompted brain development (Maryann Noonan, PhD, abstract 667.11, see attached summary).
- In situations where monkeys can potentially cooperate to improve their mutual reward, certain groups of brain cells work to accurately predict the responses of other monkeys (Keren Haroush, PhD, abstract 668.08, see attached summary).
- Following extreme social stress, enhancing brain changes associated with depression can have an anti-depressant effect in mice (Allyson Friedman, PhD, abstract 504.05, see attached summary).

Other recent findings discussed show that:

- Defeats heighten sensitivity to social hierarchies and may exacerbate brain activity related to social anxiety (Romain Ligneul, presentation 186.12, see attached speaker summary).

"Social subordination and social instability have been associated with an increased incidence of mental illness in humans," said press conference moderator Michael Platt, PhD, of Duke University, an expert in brain mechanisms involved with decision-making and social cognition. "We now have a better picture of how these situations impact the brain. While this information could lead to new treatments, it also calls on us to evaluate how we construct social hierarchies — whether in the workplace or school — and their impacts on human well-being."

This research was supported by national funding agencies such as the National Institutes of Health, as well as private and philanthropic organizations. Find more information about decision-making and the social brain at BrainFacts.org.

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Abstract 85.11 Summary

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Social Instability Slows Production of New Brain Cells in Rats

Decreased brain cell production linked to impaired cognition and increased anxiety

A new rodent study shows that living in an unstable social setting slows down the production of new brain cells — called neurogenesis — regardless of the animals' social status. Moreover, formerly dominant rats may have the most to lose, as neurological advantages associated with that status disappear in unstable environments. 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 research shows that dominant adult rats in socially stable situations have more neurogenesis in the hippocampus than subordinate rats, and subsequently improved cognition and mental health. Until now, however, the impact of social instability on new cell development was unknown. The new research, presented by Maya Opendak, of Princeton University, suggests that the stress of living in a disrupted hierarchy overrides any positive influence of social position on the formation of brain cells in adults.

"The impact of social instability in rats may provide insight into the mechanisms that cause mental illness in humans living in stressful conditions," Opendak said. "With restricted ability to produce new brain cells under stressful conditions, animals are less able to adapt and cope with social stress. This becomes a slippery slope in which mental health can quickly go from good to bad to worse."

To understand the impact of social instability on neurogenesis, researchers housed adult rats in an environment that facilitates the formation of a hierarchy. After it was in place, researchers switched the dominant animals between two communities. A revolution of sorts ensued: aggression increased and all dominant rats were displaced by former subordinates. The disruption decreased neurogenesis in the hippocampus of dominant rats, and all rats living in the unstable society produced fewer brain cells than rats living in stable conditions.

"Because decreased creation of neurons in adults has been linked to impaired cognition and increased anxiety-like behavior, our results provide new evidence for the importance of the brain's ability to adapt when dealing with social stress," Opendak said.

This research was supported with funds from the National Institutes of Health.

Scientific Presentation: Saturday, Nov. 9, 3–4 p.m., Halls B–H

85.11, Living in a disrupted social hierarchy reduces adult neurogenesis and increases oxytocin receptors in the hippocampus

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TECHNICAL ABSTRACT: In humans, socially unstable settings are associated with persistent stress and increased incidence of mental illness. Adult neurogenesis in the hippocampus has been linked to a number of functions that are relevant to mental health, including cognition, feedback of the stress response and anxiety regulation.

Previous studies have shown that living in a stable social hierarchy leads to increased neuronal growth in the hippocampus of dominant rats (Kozorovitskiy & Gould, 2004). However, no studies have investigated the impact of living in an unstable social setting on new neuron formation.

To investigate this question, we housed adult male Sprague Dawley rats in a visible burrow system (VBS), a semi naturalistic environment that facilitates the formation of a dominance hierarchy. Following formation of a stable hierarchy, dominant animals were switched between two communities. Introducing dominants into a different VBS resulted in a significant increase in aggression and changes in social status among the rats. All dominant rats lost their status as they were displaced by previous subordinates. Social disruption led to a decrease in the production of adult-born neurons in the hippocampus of dominants, a reversal of the effects of social dominance in a stable hierarchy. Furthermore, regardless of social position, rats living in an unstable hierarchy produced fewer new neurons compared to rats living in standard cages. These findings suggest that the stress of living in a disrupted hierarchy overrides any positive influence of social position on adult neurogenesis.

Because oxytocin and vasopressin have been implicated in social behavior, stress regulation and adult neurogenesis in the hippocampus (Leuner et al., 2010), we also examined the expression of oxytocin receptors in the hippocampus of rats living in disrupted social settings. We found an overall increase in oxytocin, but not vasopressin, receptor expression in the ventral, but not dorsal, dentate gyrus. Although progenitor cells and immature neurons express oxytocin receptors, social disruption produced an increase in oxytocin receptor expression primarily on mature granule cells. The extent to which oxytocin participates in effects of living in a stable or disrupted social hierarchy on adult neurogenesis remains unknown.

Abstract 667.11 Summary

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How Many Friends Can a Brain Handle?

A more extensive brain network underlies extensive social networks

A new study shows that a large network of friends and the highly developed social skills needed to manage it corresponds to certain brain regions that are bigger and better connected than in people with fewer friends. 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.

The research, led by Maryann Noonan, PhD, and conducted at the Montreal Neurological Institute, highlights the connection between social interactions and the brain. "Human beings are naturally social creatures," Noonan said. "Yet we know surprisingly little about how the brain manages our behavior within our increasingly complex social lives — or which parts of the brain falter when such behavior breaks down in conditions such as autism and schizophrenia."

Previous research revealed that brain regions associated with processing information about faces and predicting the intention of others were bigger in monkeys living in larger social groups. To test this in humans, Noonan's team scanned the brains of 18 participants, and determined the size of their social network based on the number of social interactions they reported having experienced in the past month.

Similar to the monkeys, certain regions of the brain were larger in participants with larger social networks. They also assessed the connectivity of different parts of the brain, particularly those connected through the Default Mode Network (DMN), which is thought to be involved in coordinating behavior within a social context. Studies showed that some of the brain regions that were bigger in people with larger social networks were also more strongly connected through the DMN.

The reasons behind these findings remain unclear. It could be that people with more friends use certain brain regions more frequently and as a result the areas expand to step up to the task. Alternatively, it is possible that people who were born with brains better wired to connect with others are predisposed to developing larger social networks.

This research was supported with funds from the McGill-Oxford Neuroscience Collaboration, and the Canadian Institutes of Health Research.

Scientific Presentation: Tuesday, Nov. 12, 3–4 p.m., Halls B–H

667.11, Structural and functional brain networks relating to social network size in humans

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TECHNICAL ABSTRACT: Sociability proved to be particularly adaptive for our ancestors, providing them both with a unique advantage over their competitors and their prey. The frontal lobes play a critical role in this behavior but it is increasingly apparent that other brain regions are engaged during social behaviors and that a more complete understanding requires the consideration of the social brain network as a whole. The present study sought to investigate how variations in the size of individuals' social networks are related to differences in whole brain structural grey matter (GM) in humans, and, for the first time, functional and anatomical connectivity differences.

Previous studies have suggested that social network size (SNS), a measure of social complexity, correlates with regional structural changes in cortical GM (^{1,2}). We conducted a human VBM analysis (n=18) related to self-reported 30 day social network size and report GM changes in anterior cingulate cortex (ACC), ventromedial prefrontal cortex/nucleus accumbens, amygdala, temporal polar cortex, posterior cingulate cortex/precuneus, posterior operculum and insular. Many of these regions are involved in mentalizing tasks and also are nodes of the default mode network (DMN). We compare these results to a VBM analysis conducted in macaques, using the same as Sallet et al. (2012). We now increase statistical power by expanding the sample size to 33 rhesus macaques from the original 26. Next we used dual regression to isolate the frontal component of the DMN and determined that the ACC and dorsolateral prefrontal cortex changed their functional contribution to the DMN on the basis of SNS in the same sample. Finally, we suggest that differences in functional communication are reflected in changes in the underlying white matter physiology within the cingulum bundle, superior longitudinal fasciculus, extreme capsule and arcuate fasciculus: Fractional anisotropy (FA) in these tracts correlates with SNS. We conclude the increased proficiency in social skills or social network management that presumably permit a larger SNS correlates with GM and FA, pointing to an extensive brain network underlying more extensive social networks.

¹ P.A. Lewis et al., *Neuroimage*; 57, 1624 (2011); ² J. Sallet et al., *Science*; 334, 697 (2011)

Abstract 668.08 Summary

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Making Joint Social Decisions That Don't Come Back to Bite You

As the brain makes decisions, specific brain cells work to accurately anticipate the response of others

It's not always easy to anticipate how a personal decision might affect someone else, and harder still to predict how they will respond. New animal research shows that distinct groups of brain cells are involved in decision-making that affects others, and identifies individual cells that specifically anticipate another's response in situations where mutual cooperation leads to greater rewards. The research was 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.

"The ability to make sound social decisions — in particular, decisions that are mutually beneficial — is essential to functioning well in society," said lead author Keren Haroush, PhD, a researcher at Harvard Medical School. "Understanding the cellular building blocks of social interactions may shed light on disorders in which they fall apart. Who knows how such findings may one day help the autistic child or schizophrenic adult?"

The researchers tracked activity in the anterior cingulate cortex (ACC), a part of the brain associated with reward anticipation and decision-making that is very similar among primates. They monitored the brain activity of two monkeys as they performed a game in which the reward size (the amount of juice served) depended on the decisions of both monkeys. If both monkeys made a selfish choice, the serving was small; if both made a mutually beneficial response, the serving was largest. However, if only one chose the selfish option, that monkey received the largest reward and left his opponent with the smallest portion.

Activity in ACC brain cells signaled whether or not a monkey was going to make a mutually cooperative choice, according to the study. Other cells also worked to predict the decision of the competing monkey. In separate sessions, researchers found that disrupting the ACC using electrical micro-stimulation led to a breakdown of mutual cooperation.

The results not only point to the ACC as a hot spot for social decision-making, but also as a potential locus of problems in disorders such as autism and anti-social behavior in which difficulty with social interactions are a prominent feature, and suggest the use of deep brain stimulation of the ACC as a potential treatment.

This research was supported with funds from the National Institutes of Health, Presidential Early Career Award for Scientists and Engineers, and the Whitehall Foundation.

Scientific Presentation: Tuesday, Nov. 12, 4–5 p.m., Halls B–H

668.08, Neuronal correlates of social decisions during iterative prisoner's dilemma games
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TECHNICAL ABSTRACT: Social interactions are highly dynamic, requiring animals not only to understand how their choices affect their own personal outcomes but also how their choices affect the outcomes of other animals in a group or how these animals may consequently respond. The neuronal basis for such decision-making remains poorly understood.

To investigate this processes at the neuronal level, multiple pairs of Rhesus monkey performed an iterative Prisoner's dilemma game in which each animal could either cooperate or defect in order to receive reward. Cooperation led to the highest mutual reward whereas defection led to the highest individual reward. If both monkeys defected, they both received the least possible amount.

Four monkeys and five monkey pairs performed this task, of which two underwent neuronal recordings from the dorsal anterior cingulate cortex (dACC). We find that numerous dACC neurons signaled the planned selection of cooperation over defection in relation to both one's own current and prior selections and to mutual selections. Remarkably, many neurons were also highly predictive of the opponent monkey's likely future response, and were independent of their own motor response or receipt of reward. Consistent with these physiological observations, focal disruption of dACC activity led to marked degradation in cooperation between monkeys. These findings provide new insight into the single-neuronal process by which animals make social economic decisions and anticipate the intentions of others as well as point to cingulate dysfunction as a potential locus of difficulties with such social interactions.

Abstract 504.05 Summary

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Can Too Much of a Bad Thing Be Good?

Enhancing changes in the brain associated with depression can have an antidepressant effect

New research in mice indicates that the brains of social stress-resistant individuals may be able to turn a bad thing into a good thing, on the most basic biological level. 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.

The research, presented by Allyson Friedman, PhD, of the Icahn School of Medicine at Mount Sinai, also suggests a novel approach to treatment for depression. "When under chronic stress, the brain must perform a complex balancing act, in which negative stress-related changes in the brain actively trigger positive changes. But that only happens once the negative changes reach a tipping point," Friedman said.

To investigate this phenomenon, researchers compared the brains of mice that continued to enthusiastically interact with others to those that socially isolated themselves after severe social stress — a major symptom of depression. They found a difference in the behavior of dopamine-producing brain cells found in the midbrain. In the depressed mice, these cells fired hyperactively; in the resilient mice, cells appeared to fire at a normal rate.

Further examination revealed that the dopamine-producing cells of depressed mice changed in a specific way — there was a functional increase in ion channels, called H-channels. Unexpectedly, resilient mice had even more H-channel functional increases after prolonged stress as well as an increased number of K⁺ channels. But instead of causing depression, these biological changes counteracted each other and helped stabilize psychological functioning in the resilient mice.

Researchers then demonstrated that increasing the number of H-channels in the depressed mice, which further increases dopamine firing, could trigger the production of K⁺ channels. This restored normal activity to brain cells creating dopamine and reversed depression-like symptoms in mice, who resumed their normal level of social activity.

"These results demonstrate that we can restore normal activity to midbrain dopamine neurons by dramatically increasing their firing activity," Friedman said. "This suggests a novel treatment strategy to explore for depression."

This research was supported with funds from the National Institute of Mental Health, Johnson & Johnson, and the International Mental Health Research Organization.

Scientific Presentation: Tuesday, Nov. 12, 8–11 a.m., Room 33C

504, Homeostatic plasticity of midbrain dopamine neurons mediates resilience to severe social stress

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TECHNICAL ABSTRACT: The majority of the population maintains a stable psychological functioning or resilience to depression despite exposure to prolonged stress. However, the neurophysiological basis of resilience to stress-induced depression is poorly understood. Here, in a chronic social defeat stress model of depression, we find evidence that mice resilient to the stress-induced depressive phenotype employ a novel form of homeostatic plasticity in the dopamine neurons of the mesolimbic reward circuitry.

Utilizing a combination of tyrosine hydroxylase-GFP mice and tyrosine hydroxylase-CRE mice to do cell-type-specific electrophysiology and optogenetics, we found that the plasticity of a subset of ventral tegmental area (VTA) dopamine neurons functions to compensate for the stress-induced hyperactivity found in the mice susceptible to chronic stress. Previous work has shown that a modest increase in hyperpolarization-activated cation channel-mediated current (I_h) is an ionic mechanism underlying this hyperactivity in the susceptible phenotype.

Unexpectedly we further found that the resilience phenotype, which has a control-level firing activity of dopamine neurons, showed a dramatically increased I_h. A crucial difference is that only the resilient mice showed significantly increased potassium (K⁺) channel-mediated currents. Therefore, we suggest that the increased I_h and K⁺ current function in conjunction to reduce the susceptibility inducing VTA hyperactivity. Consistent with this hypothesis, we demonstrate that a further increase of dopamine neuron hyperactivity observed in the susceptible phenotype, either by enhancing I_h or by direct optogenetic stimulation *in vivo*, induced a homeostatic increase of K⁺ currents. This induction of K⁺ currents functions to reduce the VTA hyperactivity and also behaviorally converts the susceptible phenotype to resilient.

This action of enhancing, a previously stress-inducing activity of the VTA to induce a natural resilience response is a conceptually novel antidepressant approach. Together our results demonstrate that resilience is maintained by stabilizing the activity of VTA dopamine neurons through the homeostatic balance of dramatically increased I_h and actively counteracting K^+ currents, and provide direct evidence that promoting the ionic signature of resilience in the VTA shows treatment efficacy.

Speaker Summary (186.12)

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Defeats Drive The Emergence of Social Hierarchy Representations in the Human Brain

Sunday, Nov. 10, 11 a.m.–12 p.m., Halls B–H

Why can the sting of defeat be greater than the pleasure of victory, and what are the implications?

Inter-individual competition and hierarchy are extremely important features for a number of social species, including humans. In particular, monitoring the relative strength of potential rivals and adapting behavior to avoid harmful social conflicts are two crucial abilities in primates. Social ranks influence access to food resources, sexual partners, security, and social support, which in turn determine the evolutionary fitness of the individual. These consequences of social hierarchy entail a strong selective pressure over neurobehavioral phenotypes involved in social competition.

On one side, primate research has emphasized that social hierarchies are associated with endocrinological, neurobiological, and behavioral changes observed mainly in low-status individuals. On another side, social subordination and adverse competitive contexts in humans have long been associated with depressive illness, when they are kept unresolved and when an individual is unable to adequately cope. A candidate hypothesis to explain the link between low social status and depression is that motivational profiles may be shaped by the “outcome history” of social conflicts. Numerous non-social studies have indeed highlighted a deep coupling of learning and motivational tuning processes in the brain.

Previous brain imaging experiments in social neuroscience have used predetermined and explicit social ranks and/or have associated monetary incentives with social competition. However, this approach did not allow researchers to address how social hierarchy evolves through learning via competition with opponents of unknown social ranks.

To address this question, Romain Ligneul a PhD student in Jean-Claude Dreher’s lab at the National Center for Scientific Research, recently developed a new functional magnetic resonance imaging (fMRI) experiment focusing on reward and decision-making in humans. While undergoing an fMRI, healthy males competed against three different players during a perceptual game, who, unbeknownst to them, were associated to three levels of “difficulty” (strength of the opponent). Participants progressively learned this implicit hierarchy through the frequency of their victories and defeats. Researchers measured brain activity during the game and during the presentation of the victorious or defeating outcomes in order to track the dynamics of social learning during competition — as well as the impact of the emerging social hierarchy in the so-called brain reward system.

In a subsequent behavioral experiment, Ligneul and Dreher directly tested the motivational shifts associated with changes in social status. To do so, they invited pairs of healthy males to compete in a perceptual decision-making task designed to create asymmetric frequencies of victories and defeats. Then, participants had to complete a non-social decision-making task in which they had to extract rewards and avoid punishment, allowing them to measure the differential sensitivity to positive and negative feedbacks.

The results of this study should help researchers better understand the brain mechanisms underlying defeats in competitive social settings, which may have consequences to prevent detrimental reactions in some forms of depression and may provide new clues to improve therapeutic approaches. This research may also have implications for modern social organizations, which often promotes inter-individual competition and hierarchical structures as a primary means to stimulate productivity. While the overall effect of this cultural trend is positive at the economic level, a significant proportion of the population suffers from psychological stress and distress engendered by social subordination. These findings demonstrate that a neurocomputational approach may be used to assess social decision-making processes, and that the application of these paradigms may prove useful to identify endophenotypes characterizing the neurobiological substrates underlying a number of psychiatric disorders.

This research was supported with funds from the French National Research Agency (ANR).