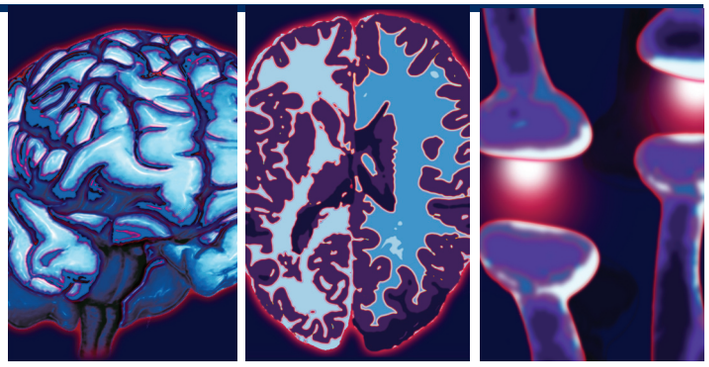


"The patient approaches the very things she should be avoiding ... It is quite remarkable that she is still alive."

Rare inability to feel fear could shed light on potential anxiety treatments

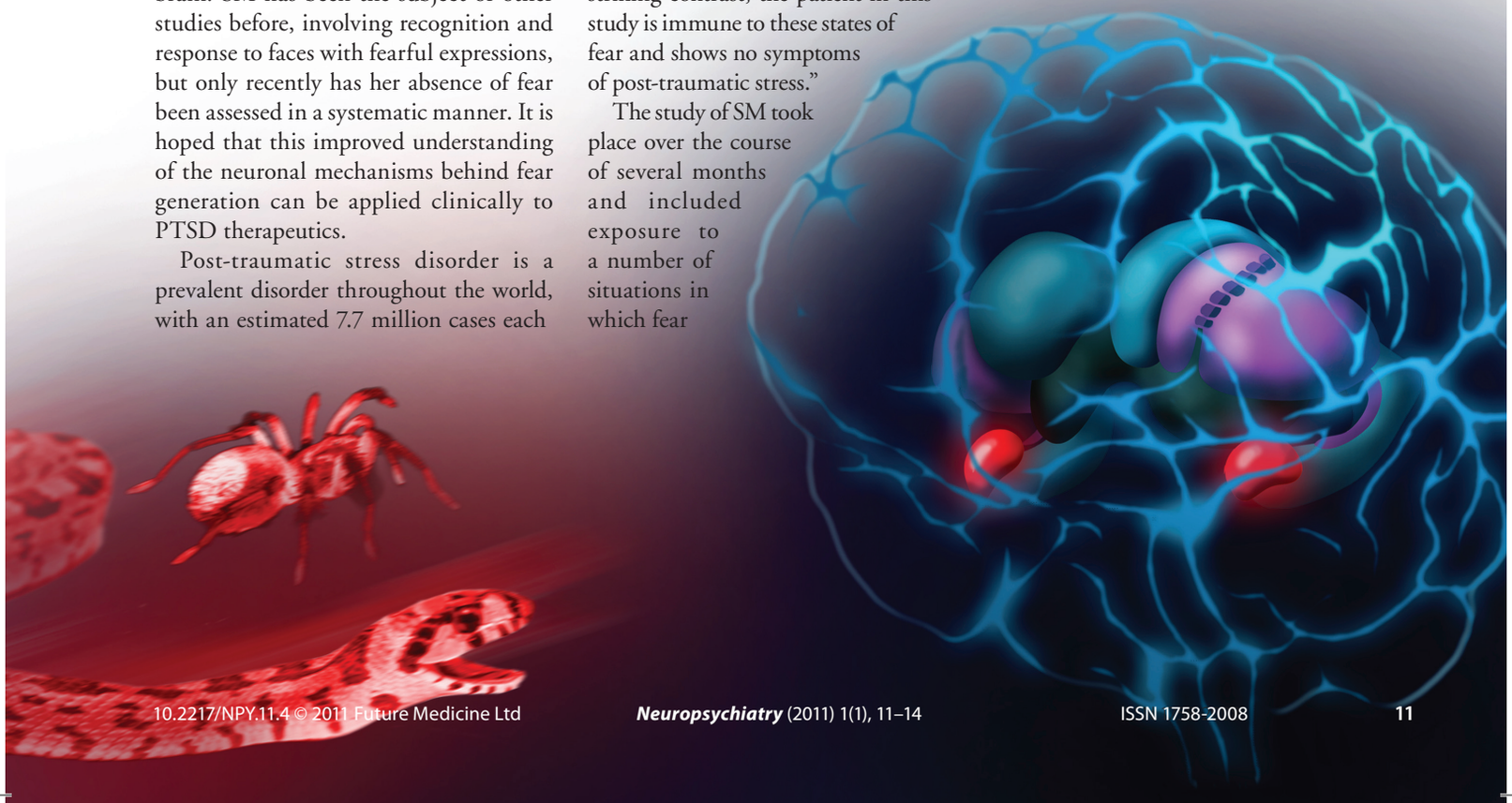
The amygdala has been implicated in the propagation of the state of fear for over 50 years. Research published recently in *Current Biology* has now given the strongest indication yet that it is also responsible for triggering the fearful state. The publication from researchers at the University of Iowa (IA, USA) could provide novel targets for studies into post-traumatic stress disorder (PTSD) therapeutics.

The recent paper focuses on a patient, referred to only as SM, with extremely rare focal bilateral amygdala lesions that have all but destroyed that region of her brain. SM has been the subject of other studies before, involving recognition and response to faces with fearful expressions, but only recently has her absence of fear been assessed in a systematic manner. It is hoped that this improved understanding of the neuronal mechanisms behind fear generation can be applied clinically to PTSD therapeutics.

Post-traumatic stress disorder is a prevalent disorder throughout the world, with an estimated 7.7 million cases each year in the USA alone. Awareness of PTSD in Western countries is correlated with overseas conflict, and as such, cases of soldiers returning from the Iraq and Afghanistan wars with PTSD have been documented.

"This past year, I've been treating veterans returning home from Iraq and Afghanistan who suffer from PTSD. Their lives are marred by fear, and they are oftentimes unable to even leave their home due to the ever-present feeling of danger," commented Justin Feinstein, lead study author and a University of Iowa doctoral student studying clinical neuropsychology. "In striking contrast, the patient in this study is immune to these states of fear and shows no symptoms of post-traumatic stress."

The study of SM took place over the course of several months and included exposure to a number of situations in which fear



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would usually be experienced. SM mentioned that for years she had tried to avoid spiders and snakes, but when exposed to them in this study, the patient was overcome with curiosity and handled them without any traces of fear, an observation found particularly interesting by study investigators. Other situations that did not elicit a fearful response were a reputedly haunted house, horror films and discussion of traumatic events in the patient's past.

"It is hoped that this improved understanding of the neuronal mechanisms behind fear generation can be applied clinically to PTSD therapeutics."

"Without our amygdala, the alarm in our brain that pushes us to avoid danger is missing," Feinstein said. "The patient approaches the very things she should be avoiding, yet, strikingly, appears to be totally aware of the fact that she should be avoiding these things. It is quite remarkable that she is still alive."

The study results are hoped to shed light on the neuronal pathways leading to the triggering of a fearful response, and are hoped to be of use in the development of therapies for anxiety-related disorders.

Source: Feinstein JS, Adolphs R, Damasio A, Tranel D: The human amygdala and the induction and experience of fear. *Curr. Biol.* 21(1), 34–38 (2011).

Brain imaging studies shed light on mechanism of action of anti-smoking medications

A number of pharmacotherapeutic treatment strategies for smoking cessation exist. So far the US FDA has approved seven medications to assist with smoking cessation including bupropion and varenicline. Recently, two studies have provided insight into the mechanism of action of both these drugs on specific brain regions in response to smoking cues.

"Researchers observed that certain brain regions were activated in response to smoking cues. Furthermore, those treated with varenicline experienced a reduction in both brain activity and reported cravings."

In one study, conducted by Christopher S Culbertson (University of California, Los Angeles, CA, USA) and colleagues, 30 nicotine-dependent smokers were randomly assigned to receive either bupropion or placebo for 8 weeks. The brain activity of all participants was then assessed in response to smoking cues.

Functional MRI scans of participants were taken within 1 week of joining the study and again at the end of the 8-week treatment period. During the scans, 45-s videos were shown that contained either smoking cues (where people were smoking in different settings), or neutral cues, with similar settings but no smoking behaviors. After watching each video, participants reported their degree of craving by using a response box.

Participants treated with bupropion reported fewer cravings in response to smoking cues compared with those who received placebo. Those taking bupropion also showed reduced activation in areas of the brain known to be associated with cravings, such as the limbic and prefrontal regions. Additionally, all participants who exhibited reduced activation in craving-related areas also experienced fewer cravings.

Based on these results, the authors concluded that: "…treatment with bupropion is associated with an improved ability to resist cue-induced craving and a reduction in cue-induced activation of limbic and prefrontal brain regions."

Similar results were reported in a second study where brain responses and cravings were assessed in response to varenicline treatment. The study was conducted by Teresa Franklin (University of Pennsylvania, PA, USA) and colleagues. The researchers examined 22 smokers who were randomly assigned to receive either varenicline or placebo for 3 weeks. Participants were shown 10 mini-video clips that contained either smoking or neutral cues and their degree of cravings was reported. Functional MRI scans were also conducted before and after the treatment period.

Researchers observed that certain brain regions were activated in response to smoking cues. Furthermore, those treated with varenicline experienced a reduction in both brain activity and reported cravings.

Both these studies reveal more about how the mechanism of action of bupropion and varenicline contributes to their clinical efficacy. The authors of the varenicline study also note that "Unsuccessful smoking cessation is more prevalent in individuals with psychiatric illness, suggesting that they have greater difficulty quitting. Varenicline and other medications that can reduce both withdrawal and cue reactivity may be of special benefit to these subgroups."

Sources: Culbertson CS, Bramen J, Cohen MS *et al.*: Effect of bupropion treatment on brain activation induced by cigarette-related cues in smokers. *Arch. Gen. Psychiatry* (2011) (Epub ahead of print); Franklin T, Wang Z, Suh JJ *et al.*: Effects of varenicline on smoking cue-triggered neural and craving responses. *Arch. Gen. Psychiatry* (2011) (Epub ahead of print).

Study results suggest that migration of interneurons from the brain's white matter to the cortex may be deficient in some patients with schizophrenia

Researchers at the Schizophrenia Research Institute (University of New South Wales, Australia) have used a specialized technique involving the staining of cells to determine the distribution of nerve cells in the brain tissue of patients with schizophrenia. The majority of cortical nerve cells, or neurons, are known to normally reside in the brain's gray matter, with only a few neurons being scattered in the white matter. However, as a result of both environmental and genetic factors, errors in neuronal migration in patients with schizophrenia are known to occur, causing a higher number of neurons to be present in the white matter of these subjects.

A recent study, published in *Biological Psychiatry*, examined the phenomenon of aberrant cellular localization of interstitial white matter neurons (IWMN) in greater detail. From a cohort of 29 schizophrenia subjects and 37 control subjects, IWMN densities were determined in the dorsolateral prefrontal cortex by counting neuronal nuclear antigen and somatostatin-positive cells.

Their results provided the first evidence that IWNM density correlates with a gray matter interneuron deficit, suggesting that migration of interneurons from white matter to the cortex may be deficient in some patients with schizophrenia.

"Our observations challenge the long-held theory that increased neurons in the white matter might be remaining from a transient layer of cells," explained lead investigators of the study, Cyndi Shannon Weickert and Samantha Fung. "We suggest that, in schizophrenia, inhibitory neurons that were travelling to the cortex might actually be stuck at some stage in their development."

However, the investigators also believe "such a theory requires further experimental evidence, such as testing the expression of markers of immature and/or migrating neurons in these IWMNs, this would be consistent with one of the leading theories of schizophrenia pathology, that is, that development of the inhibitory interneurons is altered in the brains of people with schizophrenia".

The study findings highlight the importance of brain development for the emergence of symptoms associated with schizophrenia. "This study highlights the importance for schizophrenia of better understanding the molecular switches that control the migration of nerve cells and the development of the connections between nerve cells," summarized John Krystal, Editor of *Biological Psychiatry*.

It is hoped that once scientists gather a greater understanding of the molecular factors that prevent neurons from migrating to the cortex, the development of better future treatments for schizophrenia that prevent inhibitory neurons from getting 'stuck' in the white matter can begin.

Source: Yang Y, Fung SJ, Rothwell A, Tianmei S, Weickert CS: Increased interstitial white matter neuron density in the dorsolateral prefrontal cortex of people with schizophrenia. *Biol. Psychiatry* 69(1), 63–70 (2011).

The European Commission approves paliperidone for the treatment of psychotic or manic symptoms associated with schizoaffective disorder

Janssen have announced the approval of paliperidone (INVEGA®) by the European Commission, as a treatment for psychotic or manic symptoms of schizoaffective disorder, making it the first antipsychotic treatment for this chronic and disabling mental illness. The approval is based on two Phase III studies in patients diagnosed with schizoaffective disorder. In the first study, 316 patients were assigned to receive either one or two daily doses of paliperidone, whilst in the second study, 311 patients were randomized to flexible doses of paliperidone either as monotherapy or in addition to treatment with mood stabilizers and/or antidepressants or placebo. Both trials were international, randomized, double-blind, placebo-controlled 6-week studies.

The efficacy of paliperidone was measured by the change in patients' symptoms after 6 weeks as measured by the positive and negative syndrome scale. In the first study, patients receiving the higher dose of paliperidone had a significant decrease in their symptom score compared with those receiving placebo ($p = 0.003$), whereas a significant difference was not observed in those on the lower dose ($p = 0.187$). In the second study, a significant mean decrease was also observed ($p = 0.0001$).

Furthermore, among patients with prominent manic symptoms as measured by the Young Mania Rating Scale (YMRS baseline score ≥16), paliperidone resulted in significant improvements in manic symptomatology compared with placebo.

These two studies are believed to provide important insights into this currently understudied disease.

Source: PR Newswire: http://media.prnewswire.com/en/jsp/latest.jsp?resourceid=4488589&access=EH

Study of toddlers with autism suggests that targeted intervention can benefit social skills

A recent study funded by the US NIH and published in the *Journal of Child Psychology and Psychiatry* has demonstrated potential benefits in targeted intervention programs for children with autism spectrum disorders (ASDs). In the study, researchers found that the interventions carried out improved social and communication skills in toddlers.

In the randomized trial, 50 toddlers aged between 21 and 33 months were assigned to receive one of two different interventions over 6 months. The two interventions used were identical in terms of their intensity, schedule, student-to-teacher ratio, amount of parent education, the amount of training carried out in the home by parents and instructional strategies employed; the only difference in the two groups was that one of the treatment groups included what was described by the study authors as a, "supplementary curriculum targeting socially engaged imitation, joint attention, and affect sharing." The facets of the supplementary curriculum were used as the primary end points for the study.

"Though preliminary, our findings provide promising evidence that such a supplementary curriculum can help improve social and communication skills in children younger than 3 who have ASD."

Following the 6-month intervention programs, a significant gain was found in the socially engaged imitation of toddlers that received the supplementary curriculum compared with toddlers that did not ($p = 0.02$). Gains were found for the other measures used in the trial but they did not reach statistical significance.

Commenting on the results of the study, Thomas Insel, Director of the National Institute of Mental Health said, "This new report is encouraging, as the effects on social behavior appear to provide a scaffold for the development of skills beyond the research setting … We need better early interventions for the core deficits of autism." In their published study, the authors concluded that, "Adding social engagement targets to intervention improves short-term outcome at no additional cost to the intervention. The social, language, and cognitive gains in our participants provide evidence for plasticity of these developmental systems in toddlers with ASDs."

The investigators are optimistic that the work conducted can be built upon to further help children with ASDs; the lead investigator of the trial, Rebecca Landa from Kennedy Krieger Institute (Baltimore, MD, USA), commented, "This is the first randomized controlled trial to examine an intervention focused on core social deficits of ASD in toddlers, and the first to show gains in these deficits resulting from intervention … Though preliminary, our findings provide promising evidence that such a supplementary curriculum can help improve social and communication skills in children younger than 3 who have ASD."

Source: Landa RJ, Holman KC, O'Neil AH, Stuart EA: Intervention targeting development of socially synchronous engagement in toddlers with autism spectrum disorder: a randomized controlled trial. *J. Child Psychol. Psychiatry* 52(1), 13–21 (2011).

About the News

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