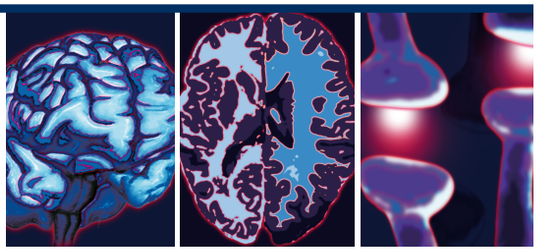
JOURNAL WATCH



Our expert panel highlights the most important research articles across the spectrum of topics relevant to the field of neuropsychiatry

Expert panel: **Jonathan E Alpert,** Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; **Jonathan M Amiel,** University College of Physicians and Surgeons and New York State Psychiatric Institute, NY, USA

Robinson OJ, Cools R, Carlisi CO, Sahakian BJ, Drevets WC. Ventral striatum response during reward and punishment reversal learning in unmedicated major depressive disorder. *Am. J. Psychiatry* doi:ajp.2011.11010137v1 (2011) (Epub ahead of print).

Multiple lines of research suggest that depression is associated with enhanced sensitivity to negative (punishing) stimuli and diminished sensitivity to positive (rewarding) stimuli across many facets of learning, memory and cognition. In this study, investigators used functional MRI (fMRI) to compare the hemodynamic response to a novel reversal learning paradigm between individuals with unmedicated major depressive disorder (MDD; n = 13) and age-matched healthy controls (n = 12). Participants were presented with stimuli (a scene and a face), one of which was associated with reward (a green smiling face) and another with punishment (a red sad face). Participants were asked to predict whether a highlighted stimulus would lead to reward or punishment while learning these associations by trial and error during an acquisition block. Reversals of these contingencies involved either an unexpected reward presented after the previously punished stimulus or by unexpected punishment presented after the previously rewarded stimulus. Although depressed subjects performed comparably well to healthy control subjects with respect to the number of punishment-related reversal errors they made, these subjects made more errors than comparison subjects on reward-related reversal trials, with a significant group × valence interaction in error rates ($F = 5.2$; $df = 1$; $p = 0.032$) indicating reduced behavioral responsiveness to reward but not punishment on this task. The *a priori* region-of-interest analysis showed significantly decreased right putamen responses on fMRI in depressed individuals compared with controls, emerging during reward- but not punishment-related reversals ($F = 10.5$; $df = 1, 25$; $p = 0.003$). The whole-brain fMRI analysis also showed significantly decreased responses in the anteroventral putamen in depressed subjects compared with controls during reward-related but not punishment-related reversal trials. Attenuated reward-related striatal responses in MDD subjects is consistent with the results of several previous studies by this group and others. Notably, however, previous studies of reversal learning performance using traditional paradigms

Journal Watch highlights some of the most important papers recently published in the field of neuropsychiatry and research. The editorial team welcomes recommendations for relevant papers for inclusion in future issues.
Please direct your suggestions to:
Jonathan Tee, Commissioning Editor
j.tee@futuremedicine.com

10.2217/NPY.11.68 © 2011 Future Medicine Ltd **Neuropsychiatry** (2011) 1(6), 529–532 ISSN 1758-2008

in which reward- and punishment-associated components were not separated had failed to implicate striatal involvement in MDD. Using a newer paradigm, the current study has helped resolve this discrepancy by disentangling reward- and punishment-related reversal learning and showing striatal involvement in reversal learning deficits specifically related to reward. As the study compared subjects who were currently depressed compared with healthy controls who never experienced MDD, no inferences are possible regarding the relative roles of state versus trait. Nevertheless, using a novel reversal learning paradigm, this study extends previous work implicating a crucial role of the anteroventral striatum and associated circuits involving afferent projections from the orbitofrontal cortex, amygdala and mesostriatal dopamine pathways in hedonic processing and neurocognitive deficits in depression.

– Written by Jonathan E Alpert

Berk M, Dean O, Cotton SM *et al.* The efficacy of *N*-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial. *J. Affect. Disord.* 135(1–3), 389–394 (2011).

A role for redox dysregulation in the pathophysiology of bipolar disorder has been suggested based upon data on the effects of oxidative stress on cellular constituents including lipids, proteins and DNA together with structural evidence for a neurodegenerative process in bipolar disorder, evidence for impaired oxidated defenses in patients with bipolar disorder, evidence that many known bipolar treatments appear to have significant impacts on oxidative processes and association studies implicating polymorphisms of key genes in the glutathione pathway in bipolar disorder. Glutathione is the primary endogenous antioxidant in the brain and may be depleted in oxidative stress states. Enhancing the supply of L-cysteine, the rate-limiting factor in glutathione synthesis, via a precursor, *N*-acetylcysteine (NAC), which appears to cross the blood–brain barrier, leads to a rise in brain glutathione levels. Given the paucity of safe and effective treatments for bipolar depression, the investigators evaluated the efficacy of an 8-week open-label adjunctive trial of NAC (1 g twice daily) among 149 individuals with bipolar disorder with moderate depression. The acute open-label phase was followed by a randomized placebo-controlled trial of NAC for maintenance treatment that will be reported separately. Eligible participants met DSM-IV criteria for bipolar I (69.6%), bipolar II (29.7%) and bipolar not otherwise specified (0.7%) and were required to have a Montgomery–Asberg Depression Rating Scale (MADRS) score of ≥12 at the time of study entry. Retention rates were high in the acute phase, with an 88.6% completion rate. There was significant improvement on the Bipolar Depression Rating Scale (mean change: 8.7 points; $p < 0.001$), the primary outcome measure, as well as on other measures including the MADRS, Young Mania Rating Scale, Quality of Life Enjoyment and Satisfaction Questionnaire and Global Assessment of Functioning. There was also significant improvement on the Clinical Global Improvement Scale (CGIS) both overall and for depression, although not for mania. The chief limitation of the acute treatment study is the absence of a placebo arm. Other limitations include lack of information on side effects and on concurrent treatments including mood stabilizers, antidepressants and psychosocial therapies. Nevertheless, the data are consistent with a previous 6-month controlled trial in a smaller sample of bipolar subjects that showed efficacy. The study also adds to the limited literature suggesting efficacy of NAC in other psychiatric disorders including schizophrenia, obsessive–compulsive disorder and cocaine dependence. Evidence that NAC may protect against oxidative stress, enhance neurogenesis and exert anti-inflammatory effects has contributed to the ongoing interest in this agent in the treatment of psychiatric disorders.

– Written by Jonathan E Alpert

Chaudieu I, Norton J, Ritchie K, Birmes P, Vaiva G, Ancelin ML. Late-life health consequences of exposure to trauma in a general elderly population: the mediating role of reexperiencing posttraumatic symptoms. *J. Clin. Psychiatry* 72(7), 929–935 (2011).

Previous studies suggest a link between exposure to traumatic events and poorer physical health, although most of these studies have used self-report measures of perceived health, focused on combat trauma and have not generally enrolled older subjects, a population that is at particular risk for physical health problems and in whom longer-term effects of trauma may be more evident. This retrospective study focused on the long-term consequences of a lifetime exposure to trauma on health in a French elderly general population group using data from a longitudinal study (the Enquête de Santé Psychologique – Risques, Incidence et Traitement [ESPRIT]) of community-dwelling participants. Psychiatric health, medical history and clinical examination (International Classification of Disease [ICD]-10 criteria) were assessed in 1662 subjects (mean age: 72.5 years; 59% women). Lifetime traumatic exposure, post-traumatic stress disorder (PTSD) and psychiatric diagnoses were obtained using the Watson PTSD Inventory and the Mini-International Neuropsychiatric Interview. The outcome measures used were the Mini-International Neuropsychiatric Interview, Center for Epidemiologic Studies Depression Scale, Mini-Mental State Examination and measures of physical health obtained on a detailed, standardized health interview. More than half of subjects (59.3% men and 53.7% women) reported experiencing a traumatic event meeting DSM-IV criterion A1, with a lifetime and current prevalence of PTSD of 2.4 and 1.2%, respectively. Based on the low prevalence of PTSD *per se*, investigators focused on one aspect of the PTSD syndrome, namely re-experiencing symptoms. Of 870 subjects who reported a history of trauma, 258 (29.7%) reported recurrent re-experiencing symptoms. Trauma was associated with a greater number and

severity of health-related outcomes, particularly cardiovascular diseases, including angina pectoris (p = 0.002) and hypertension (p = 0.054), with nontraumatized subjects having the lowest risk and those with both trauma and recurrent re-experiencing of events having the highest risk. Trauma with re-experiencing was also associated with greater risk of current major depression (p < 0.0001), anxiety disorder (p = 0.032), psychiatric comorbidity (p = 0.002) and lifetime suicide attempts (p = 0.009) compared with nontraumatized subjects. Trauma without re-experiencing was not associated with elevated rates of psychiatric disorders and, indeed, subjects experiencing trauma without re-experiencing symptoms showed somewhat lower rates of multiple psychiatric comorbidities (p = 0.035) and suicidal ideation (p = 0.054) than even subjects without a trauma history. Limitations of the study include the use of retrospective reporting of trauma with possible recall bias, as well as the lack of data on the number of lifetime traumatic events, given the possibility that recurrence of trauma may be relevant to both risk of developing re-experiencing symptoms and to cumulative health impacts. Moreover, an argument the investigators advance for special resiliency among those subjects exposed to trauma who did not develop re-experiencing symptoms compared with those not exposed to trauma is based on a very small number of significant health differences between these two groups, which may be spurious given multiple comparisons. Nevertheless, this study indicates a high prevalence of lifetime trauma in the general population, extends the literature on the physical and mental health sequelae of trauma to an elderly, civilian population and suggests that re-experiencing symptoms after trauma may be a harbinger of health impacts, even among individuals without syndromal PTSD.

– Written by Jonathan E Alpert

Krystal JH, Rosenheck RA, Cramer JA *et al.* Veterans Affairs Cooperative Study No. 504 Group. Adjunctive risperidone treatment for antidepressant-resistant symptoms of chronic military service-related PTSD: a randomized trial. *JAMA* 306(5), 493–502 (2011).

In this double-blind, randomized, placebo-controlled trial of adjunctive risperidone for the treatment of military service-related post-traumatic stress disorder (PTSD), Krystal and colleagues investigated the efficacy of the often-employed off-label use of second-generation antipsychotics for individuals whose PTSD symptoms did not improve with serotonin-reuptake inhibitors. Subjects included 247 adult veterans who met diagnostic criteria for military service-related chronic PTSD and showing little or no response to at least two adequate trials of serotonin-reuptake inhibitors. The study excluded people with bipolar disorder, schizophrenia and substance-use disorders. Subjects continued their baseline pharmacotherapy and were randomized to receive adjunctive risperidone (up to 4 mg/day) or placebo and were followed for 6 months, with serial ratings on the 34-item Clinician-Administered PTSD Scale (CAPS) being obtained.

As a group, the study subjects were mostly male (97%), middle-aged (mean age: 54 years), non-Hispanic white (66%), had combat experience dating to the Vietnam war or earlier (72%), had lifetime diagnoses of major depression (70%) and alcohol abuse or dependence (63%), received disability compensation (84%) and were highly symptomatic at baseline (CAPS: 78 ± 15). The group randomized to risperidone had a mean decrease in CAPS score of 16, while the group randomized to placebo had a mean decrease in CAPS score of 13, a difference that was not statistically significant. In *post hoc* analyses, risperidone treatment was associated with statistically significant but clinically modest symptom reduction on the re-experiencing and hyperarousal, but not the avoidance/numbing subscales of the CAPS.

This is an important negative study. Although the investigators encountered methodologic difficulties, including lower-than-expected subject recruitment and an exclusion of 10% of subjects' data due to the loss of source documentation, they also had balanced subject loss and greater-than-expected subject retention that maintained the study's power to detect a modest difference in CAPS score. Thus, the study appears to be successful and its negative results appear to be meaningful. This study disconfirms the efficacy of using adjunctive risperidone for treatment-refractory PTSD. However, these findings are limited to a military population with chronic illness and does not generalize to treatment with other second-generation antipsychotics.

– Written by Jonathan M Amiel

Rees S, Silove D, Chey T *et al.* Lifetime prevalence of gender-based violence in women and the relationship with mental disorders and psychosocial function. *JAMA* 306(5), 513–521 (2011).

In this Australian cross-sectional study, Rees and colleagues characterized the association between gender-based violence (GBV), including intimate partner physical violence, rape, sexual assault and stalking, and rates of psychiatric illness and functional impairment among women. The investigators queried the Australian Bureau of Statistics' Second National Mental Health and Well-Being Survey, conducted in 2007. A nationally representative sample of 14,805 households was identified through random stratification and multistage probability sampling. Of these, 8841 individuals participated in the study, which included an in-person, computer-assisted interview using the World Mental Health – Composite International Diagnostic Interview version 3.0 (WMH–CIDI 3.0). The instrument was used to identify disorders of anxiety, mood, substance use and, individually, post-traumatic stress disorder (PTSD). The instrument also identified a wide range of GBV, including physical violence, rape, nonrape sexual assault and stalking.

Of the 4451 women surveyed, the lifetime prevalence of mental disorders was 38%, with a lifetime prevalence of 25% for anxiety disorders, 18% for mood disorders, 14% for substance-use disorders and 10%

for PTSD. The lifetime prevalence of one or more form of GBV was 27%, with 8% of the women reporting physical violence, 8% reporting rape, 15% reporting nonrape sexual assault and 10% reporting stalking.

This study provides robust, although unsurprising evidence. There were high correlations between the prevalence of the four forms of GBV, suggesting that women exposed to one form were at higher risk of experiencing other forms of GBV. Exposure to GBV was associated with increased rates of mental disorders – with a notable twofold increase in PTSD – along with increased rates of physical disorders and functional impairment. Although the methodology of the study necessarily limits the generalizability of its findings as purely associational and applicable to individuals living in private residences in a relatively wealthy country, it does provide a powerful call for longitudinal studies investigating the personal and societal impact of GBV and for the development of interventions to curb its prevalence.

– Written by Jonathan M Amiel

Stroup TS, McEvoy JP, Ring KD *et al.*; The Schizophrenia Trials Network. A randomized trial examining the effectiveness of switching from olanzapine, quetiapine, or risperidone to aripiprazole to reduce metabolic risk: comparison of antipsychotics for metabolic problems (CAMP). *Am. J. Psychiatry* 168(9), 947–956 (2011).

In this multisite randomized controlled trial, Stroup and colleagues evaluated the efficacy and practicality of switching from commonly used antipsychotic medications associated with the development of cardiovascular disease (olanzapine, quetiapine and risperidone) to a medication with a lesser risk of metabolic side effects (aripiprazole). Subjects included adults with schizophrenia that was well controlled on olanzapine, quetiapine or risperidon monotherapy, whose BMI exceeded 26 and whose non-high-density lipoprotein (HDL) cholesterol was equal to or greater than 130 mg/dl. The subjects were randomized to stay on their regimen or switch to aripiprazole (5–30 mg daily) through a 4-week cross-taper schedule. All participants also received a manualized behavioral intervention for improving exercise and dietary habits. Metabolic effects were assessed by serial measurements of non-HDL cholesterol and weight. Clinical effects were measured by serial assessments with the Positive and Negative Symptom Scale (PANSS), the Clinical Global Impression (CGI) scale and rates of treatment discontinuation. The study defined efficacy failure as psychiatric hospitalization, a 25% increase in PANSS score or ratings of much worse or very much worse on the CGI.

Two hundred and fifteen subjects were randomized, 213 received their assigned treatment and 187 remained in the study beyond the first 4 weeks and were included in the efficacy analysis. Metabolically, switching to aripiprazole was associated with a reduction of non-HDL of 20 mg/dl compared with a decrease of 10 mg/dl for those who remained on their baseline regimen ($p = 0.01$), and mean weight loss of 0.8 kg (standard deviation: 1.4 kg) in the switchers compared with 0.1 kg (standard deviation: 1.0 kg) for those who did not switch. Clinically, the two groups had no difference in PANSS scores and their rates of efficacy failure were similar (21% for switchers and 17% for nonswitchers), but over the course of the study, nearly twice as many switchers discontinued their protocol-specified treatment (48%) compared with nonswitchers (27%), and the switchers had higher rates of adverse events (17%) compared with nonswitchers (9%).

Based on these data, the investigators concluded that switching to an antipsychotic medication with lower risks of metabolic side effects is reasonable in the setting of careful cross-titration and close monitoring. However, given the high rates of discontinuation in the switchers, a narrower conclusion – that the metabolic benefits of switching come at the risk of discontinuation – may be germane for clinicians and patients facing this conundrum.

– Written by Jonathan M Amiel

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.