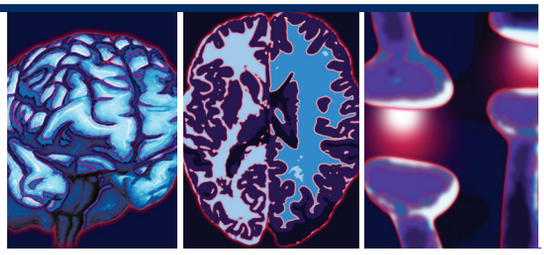
JOURNAL WATCH



Our panel of experts highlight 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; **Joan Daughton,** UNMC Department of Child and Adolescent Psychiatry, Nebraska Medical Center, Omaha, NE, USA; **Leonardo F Fontenelle,** Programa de Ansiedade e Depressão, Instituto de Psiquiatria, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil

Skodol AE, Grilo CM, Keyes KM, Geier T, Grant BF, Hasin DS: Relationship of personality disorders to the course of major depressive disorder in a nationally representative sample. *Am. J. Psychiatry* 168, 257–264 (2011).

Although a number of clinical trials, naturalistic studies and meta-analyses, as well as the experience of many clinicians, have suggested that personality disorders exert a negative effect on the treatment outcome of major depressive disorder, there are conflicting results in the literature probably owing to methodological limitations, including small sample sizes, lack of standardized diagnostic interviews and retrospective or cross-sectional designs. Exploiting the National Epidemiologic Survey on Alcoholism and Related Conditions (n = 43,093), the largest prospective psychiatric epidemiologic survey ever undertaken and one which systematically assessed personality disorders, Skodol and colleagues were able to identify 1996 respondents who were diagnosed with major depressive disorder (MDD) in the first wave of in-person interviews (2001–2002) and re-interviewed 3 years later with the Alcohol Use Disorder and Associated Disabilities Interview Schedule, *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV version, which incorporated items from the Structured Clinical Interview for DSM-IV Personality Disorders. A little over 15% of individuals with MDD showed persistence of syndromal depression across the two waves of interviews. Among Axis I disorders, both anxiety disorders and dysthymic disorder significantly predicted persistence of MDD. On univariate analysis, various personality disorders (avoidant, borderline, histrionic, paranoid, schizoid and schizotypal) were also associated with elevated risk of depressive persistence. However, following a series of multivariate tests of predictors that allowed for disentangling the contributions of multiple possible confounding factors (e.g., other Axis I comorbidity, other personality disorders, age of depressive onset and duration of MDD episode), among the personality disorders only borderline personality disorder robustly predicted persistence of MDD. As pointed out by the authors as well as Myrna Weissman in an accompanying editorial, limitations of this study include the use of lay interviewers, over-representation of Caucasian, college-educated and married respondents, naturalistic treatment, lack of assessment of alternative dimensional models of personality, and assessment of most individual personality disorders in the first or second wave of interviews but not in both. Nevertheless, this study represents the most rigorous demonstration to date of borderline personality disorder as a powerful risk factor for MDD persistence. On the eve of DSM-5, this study also contributes to a rich dialog on the interconnections between Axis I and Axis II conditions that involve mood dysregulation.

Information resource

1 Weissman MM: Can epidemiology translate into understanding major depression with borderline personality disorder? *Am. J. Psychiatry* 168, 231–233 (2011).

News & Views

News

Journal Watch

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Bella T, Goldstein T, Axelson D *et al.*: Psychosocial functioning in offspring of parents with bipolar disorder. *J. Affective Disord.* DOI: 10.1016/j.jad.2011.03.022 (2011) (Epub ahead of print).

A number of major studies have demonstrated psychosocial difficulties among offspring of parents with major depressive disorder. Although fewer studies have assessed psychosocial problems among offspring of parents with bipolar disorder, a small number of studies suggest increased behavioral problems and psychopathology. In this study, the authors compared the psychosocial functioning of three groups of children (ages 6–18 years) enrolled in the Pittsburgh Bipolar Offspring Study (BIOS): offspring of probands with bipolar disorder (n = 388), offspring of probands with other types of psychopathology (n = 132), including major depressive disorder, anxiety disorders and/or substance use disorders, and offspring of healthy probands (n = 118). Psychosocial functioning was assessed at study intake using the schedule of the Adolescent Longitudinal Interval Follow-Up Evaluation (A-LIFE), the Child Behavior Check List (CBCL) and the Children's Global Assessment Scale (CGAS). Psychopathology was diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV criteria through parent and offspring interviews using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (K-SADS-PL). Offspring of probands with bipolar (BP) disorder had higher rates of nearly every lifetime Axis I disorder examined (particularly bipolar spectrum disorder, depression, anxiety, attention deficit hyperactivity disorder and disruptive behavioral disorders) than offspring in either of the other two offspring groups. With respect to A-LIFE evaluation, offspring of probands with BP disorder had significantly poorer scores on three subscales (satisfaction, recreation and interpersonal) and on the total score when compared with the other two groups. On the work subscale, offspring of probands with BP disorder had worse functioning in comparison with the offspring of healthy probands but not in comparison with the offspring of probands with non-BP disorder psychopathology. With respect to CBCL measures, offspring of probands with BP disorder had significantly lower scores on all subscales (Activities, Social and School) than the offspring of healthy probands. There was no significant difference in functioning between offspring of probands with BP disorder and offspring of probands with non-BP psychopathology on the CBCL subscales. With respect to the GCAS, offspring of probands with BP disorder had significantly lower scores (current, highest past, and most severe past) than the other two groups. Nevertheless, most psychosocial impairments of offspring of BP disorder parents were in the mild range consistent with previous analyses, which have generally shown mild-to-moderate impairment among these offspring. Moreover, proband parent functioning and offspring DSM-IV psychopathology emerged as the two most salient variables accounting for the differences in offspring psychosocial functioning between groups. When these were controlled for, there were minimal differences among offspring of the three proband groups. Although the study is limited by its cross-sectional design, naturalistic treatment (e.g., 30% of offspring of BP probands were receiving psychosocial and/or pharmacological treatment), the young age of the offspring (mean approximately 11 years old) and significant demographic differences across groups, including race and family composition, this study suggests that interventions to improve parental functioning and to treat offspring psychopathology may help reduce the risk for long-term functional impairment in offspring of parents with BP disorder.

Hausner L, Damian M, Sartorius A, Frolich L: Efficacy and cognitive side effects of electroconvulsive therapy (ECT) in depressed elderly inpatients with coexisting mild cognitive impairment or dementia. *J. Clin. Psychiatry* 72(1), 91–97 (2011).

Geriatric depression often co-occurs in the setting of comorbid cerebrovascular or neurodegenerative diseases. Electroconvulsive therapy (ECT) is frequently considered for treatment of severe depression in this population, although it is known to cause cognitive difficulties including reversible confusion as well as retrograde and transient anterograde memory impairment in nongeriatric or heterogeneous populations. This small study (n = 44) addressed the question of whether ECT worsens cognition in geriatric patients (> 65 years) with premorbid mild cognitive impairment (MCI; n = 19) or dementia (n = 12) compared with geriatric patients without pre-existing cognitive impairment (no cognitive impairment [NCI]; n = 13). Depressive symptoms were assessed with the 21-item Hamilton Depression Rating Scale (HDRS)-21, while cognition was assessed with the Mini-Mental State Examination (MMSE). The groups had similarly severe depression at baseline and similar depression improvement at 6 weeks after the last ECT. As expected, the dementia group had significantly lower pre-ECT MMSE scores than the NCI group. All groups had cognitive decline (albeit nonsignificant) during ECT as measured by the MMSE. However, the NCI group had significant MMSE improvement over pre-ECT baseline at both 6 weeks and 6 months after the last ECT. The MCI group had MMSE decline at 6 weeks post-ECT but significant improvement at 6 months. The dementia group had no significant long-term changes during 6 month follow-up in MMSE, although numerically the dementia group on antidementia treatment (rivastigmine, memantine) showed cognitive improvement 6 weeks after ECT while the dementia group not receiving treatment showed decline. The study is limited by small sample sizes, absence of a non-ECT comparator condition and use of the MMSE, a relatively coarse measure of cognitive function. Nevertheless, this study suggests that ECT is equally effective for

treating depression in subjects with MCI or dementia as compared with noncognitively impaired geriatric patients and that while premorbid cognitive decline is associated with greater likelihood of MMSE decline at 6 weeks post-ECT, cognition as measured by the MMSE is generally preserved or enhanced by 6 months post-ECT in all subjects regardless of premorbid cognitive status.

Handen BL, Johnson CR, McAuliffe-Bellin S *et al.*: Safety and efficacy of donepezil in children and adolescents with autism: neuropsychological measures. *J. Child Adolesc. Psychopharmacol.* 21(1), 43–50 (2011).

Recently published studies have suggested that cholinesterase inhibitors may enhance behavioral functioning, language, social behavior and core features of autism spectrum disorder. However, limited focus has been placed on the effects of these agents on executive functioning. The current study is one of the first to investigate changes in neuropsychological functioning. A total of 34 children and adolescents (between 8 and 17 years of age) with autism spectrum disorder were enrolled. All children in this study had an IQ over 75 (mean ~96). This 10-week, double-blind, placebo-controlled study investigated donepezil at doses of 5 and 10 mg. The mean severity of autism on the Autism Diagnostic Observation Schedule (ADOS) was approximately 11. Overall, donepezil was tolerated well with mild increases in diarrhea, headache and fatigue. There were no severe adverse events. A robust placebo effect was noted in this study, which may be attributable to the learning effects seen after multiple exposures to the assessment tools. Subjects in this study seemed to improve at both dose levels, however, no statistically significant improvements were seen on performance overall. The results of this trial are inconsistent with previous reports on this topic. In comparison to other positive studies, the children in this study were older. This may suggest that cognitive enhancers have their greatest efficacy among younger children still in early stages of development. In this study, few subjects displayed global deficits in cognitive functioning at baseline, which may have made significant gains after treatment difficult to obtain. Additional trials that focus on specific executive functioning deficits and select subjects with weaknesses in those areas are required. Also, a more extended study may be more beneficial to allow ample time for treatment to be effective.

Nagel BJ, Bathula D, Herting M *et al.*: Altered white matter microstructure in children with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatr.* 50(3), 283–292 (2011).

Few studies have looked at white matter microstructure in pre-adolescent children with attention deficit hyperactivity disorder (ADHD). If microstructure abnormalities can be confirmed in samples of younger children, their importance as biomarkers and their potential for eventual clinical translation will be markedly enhanced. In this study, 20 children with ADHD were compared with 16 healthy children, ages 7–9 years, using diffusion tensor imaging. The children were largely medication naive and free of comorbidity. Results of this study confirm that microstructure in long-range white matter pathways shows abnormalities before adolescence in children with ADHD. Although the effects were widespread, the cortical regions connected by the tracts have been implicated in ADHD and associated cognitive dysfunction. In fact, this study confirmed that connections between the cerebellum and associated structures are different in ADHD. Given similar results from other studies in older children and adults, cerebellar white matter abnormalities may be a robust and stable feature of ADHD. The findings further suggested that aberrant or delayed myelin development appears to exist in ADHD. Later maturing frontolimbic pathways were abnormal in children with ADHD, likely due to delayed or decreased myelination. This has not previously been found in adolescent or adult stages of the disorder. From this study, it is possible to say that disruptions in white matter microstructure may play a key role in the early pathophysiology of ADHD. Alterations in late-maturing frontolimbic pathways, seen in the present study but not in older samples, may indicate an early dynamic marker that can provide additional clues to the pathophysiology of ADHD. It is postulated that ADHD might entail an altered developmental trajectory in the structural connectivity of the brain with neuroanatomic markers specific to development.

Gunderson JG, Stout RL, McGlashan TH *et al.*: Ten-year course of borderline personality disorder: psychopathology and function from the collaborative longitudinal personality disorders study. *Arch. Gen. Psychiatry* DOI: 10.1001/archgenpsychiatry.2011.37 (2011) (Epub ahead of print).

Traditionally, borderline personality disorder (BPD) is considered to be chronic and intractable. Gunderson *et al.* aimed at probing this assertion by comparing the natural course and the social functioning of 175 patients with BPD to that of 312 patients with cluster C personality disorders and 95 patients with major depressive disorder (MDD) but no personality disorder. The sample comprised treatment-seeking 18–45-year-old patients from 19 different clinical settings (hospital and outpatient) who were followed for 10 years with the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV Axis I Disorders, the Diagnostic Interview for DSM-IV Personality Disorders-Follow-Along Version and the Longitudinal Interval Follow-up Evaluation. In total, 85% of patients with BPD remitted. Remission of BPD was slower than for MDD and marginally slower than for other cluster C personality disorders. The relapse rate of patients with BPD was 12%, a lower rate than that shown by patients with MDD and other personality disorders. Furthermore, social functioning scores indicated severe

impairment with only modest, albeit statistically significant improvement over time. Patients with BPD remained persistently more dysfunctional than the other two groups. The authors concluded that the 10-year course of BPD is characterized by high rates of remission, low rates of relapse, but severe and persistent impairment in social functioning.

Olabi B, Ellison-Wright I, McIntosh AM, Wood SJ, Bullmore E, Lawrie SM: Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. *Biol. Psychiatry* DOI: 10.1016/j.biopsych.2011.01.032 (2011) (Epub ahead of print).

Although schizophrenia has been associated consistently with structural brain abnormalities, it still unclear whether these changes are static or progressive. To clarify this issue, Olabi and coworkers reviewed data from 27 longitudinal volumetric studies using region of interest structural MRI in 928 patients with schizophrenia and 867 healthy individuals. More specifically, they assessed the percentage change in volume between scans for 32 brain regions of interest and combined the data using random effects meta-analysis. The time between baseline and follow-up MRI scans ranged from 1 to 10 years. Olabi *et al.* reported that patients with schizophrenia exhibited significantly greater reductions over time in whole-brain volume, whole brain gray matter, frontal gray and white matter, parietal white matter and temporal white matter volume, as well as larger increases in lateral ventricular volume, than healthy control subjects. Of note, the differences between patients with schizophrenia and healthy controls in terms of percentage volume change were -0.07% for whole-brain volume, -0.59% for whole-brain gray matter, -0.32% for frontal white matter, -0.32% for parietal white matter, -0.39% for temporal white matter and +0.36% for bilateral lateral ventricles. The authors argued that schizophrenia is associated with progressive structural brain abnormalities affecting both gray and white matter.

Siegle GJ, Steinhauer SR, Friedman ES, Thompson WS, Thase ME: Remission prognosis for cognitive therapy for recurrent depression using the pupil: utility and neural correlates. *Biol. Psychiatry* 69(8), 726–733 (2011).

There is a pressing need to identify predictors of response of patients with major depressive disorder (MDD) to specific psychotherapeutic and/or pharmacological treatments. Since pupillary response to emotional information is an inexpensive and noninvasive parameter reflecting limbic reactivity and executive control, it could, in theory, help match patients with appropriate treatments. In this study, Siegle and coworkers evaluated whether pretreatment pupillary responses to emotional stimuli predicted response to 16–20 sessions of cognitive therapy in a cohort of 32 patients with MDD. Furthermore, 20 patients and 51 healthy controls were assessed on the same task using functional MRI. The authors found that symptom remission was associated with the combination of higher initial severity and low sustained pupillary responses to negative words. They also reported that increased pupillary responses were associated with increased activity in dorsolateral prefrontal regions associated with executive control and emotion regulation. The authors argued that, for patients with MDD and higher severity of symptoms, disruptions of executive control mechanisms responsible for initiating emotion regulation, which are indexed by low sustained pupil responses and targeted in therapy, may play an important role in treatment response to cognitive therapy.

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