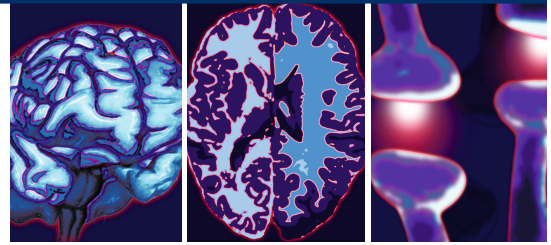


JOURNAL WATCH



Our experts 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 Amiel, Department of Psychiatry, Columbia University College of Physicians & Surgeons, NY, USA; Joan Daughton, UNMC Department of Child & Adolescent Psychiatry, Nebraska Medical Center, NE, USA

Wolff JJ, Gu H, Gerig G *et al.* Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am. J. Psychiatry* doi:10.1176/appi.ajp.2011.11091447 (2012) (Epub ahead of print).

A link between autism spectrum disorders (ASDs) and aberrant neural circuitry including abnormal white-matter development has been supported by multiple studies. To further clarify the nature and developmental course of this association, the investigators conducted the first prospective, longitudinal study of white matter fiber tract development of infants at high risk for autism by virtue of having an older sibling with autism. The focus was on 15 white matter tracts selected on the basis of reported associations with ASDs or their core behavioral features including the anterior limb of the internal capsule, anterior thalamic radiation, corpus callosum, fornix, inferior longitudinal fasciculus, posterior limb of the internal capsule and the uncinate. Ninety two infants were studied at ages 6, 12 and 24 months. Infants were assessed with diffusion-weighted MRI scans and behavioral assessments including the Autism Diagnostic Observation Schedule. Based on the ASD cut-off score on the latter scale, infants were divided into positive- and negative- ASD groups. At the age of 24 months, 28 infants met criteria for ASD and 64 did not. There were no demographic differences between the two groups and both groups showed

significant increases in fractional anisotropy between 6–24 months. However, the developmental trajectories of the fractional anisotropy values for 12 of the 15 fiber tracts studied differed significantly between the groups, with most of the fiber tracts for the ASD-positive infants characterized by higher fractional anisotropy at 6 months followed by blunted developmental trajectories thereafter, such that fractional anisotropy values at 24 months were lower for infants with ASD than those without. The finding of lower fractional anisotropy values by the age of 24 months is consistent with other studies in older children and adolescents with ASDs. The study is significant for showing the earliest known brain differences associated with the subsequent development of ASDs. The altered trajectories of development demonstrated in this study appear to precede the onset of clinical symptoms suggesting both the possibility of a causal relationship and the potential promise of imaging biomarkers for identifying risk of ASDs at a very early age when behavioral or biological interventions may be implemented to alter the course of the disorders. Moreover, if replicated, the intriguing finding of initially higher fractional anisotropy at 6 months followed by blunted trajectories may shed light on the pathophysiology of these disorders. Future work is needed to extend longitudinal neuroimaging to younger infants as well as older children and to study a comparison population of subjects who do not carry familial risk for ASDs. – Written by Jonathan E Alpert

News & Views

News

Journal Watch

Ask the Experts

Hollander E, Soorya L, Chaplin W et al. A double-blind placebo-controlled trial of fluoxetine for repetitive behaviors and global severity in adult autism spectrum disorders. *Am. J. Psychiatry* 169(3), 292–299 (2012).

Several lines of evidence have suggested a role for abnormal serotonin transmission in autism spectrum disorders (ASDs) and for serotonergic agents in their treatment. These include findings of elevated platelet serotonin and polymorphisms of the serotonin transporter gene in a subset of individuals with these disorders. Randomized control trials of serotonin reuptake inhibitors (SSRIs) in ASDs have yielded mixed results. A single-site study of low-dose fluoxetine in children showed significant improvement of core behavioral symptoms of ASDs with minimal side effects while a multi-site trial of citalopram in children with ASDs failed to show efficacy and found worrisome side effects including worsening of stereotypical behaviors. In a previous trial of adults with ASDs, the SSRI fluvoxamine was found to reduce repetitive behaviors and associated symptoms including aggression and anxiety with few side effects. In the current study, the investigators evaluated the effects of fluoxetine and placebo on repetitive behaviors and global severity in adults with ASDs. Subjects with ASDs were enrolled in a 12-week double-blind placebo-controlled fluoxetine trial. Thirty seven were randomly assigned to fluoxetine ($n = 22$) or placebo ($n = 15$). Doses started at 10 mg/day and were increased rapidly as they were tolerated up to 80 mg/day within the first 4 weeks. Repetitive behaviors were measured with the compulsion subscale of the Yale–Brown Obsessive Compulsive Scale; the Clinical Global Impression improvement scale was used to rate improvement in obsessive–compulsive symptoms and overall severity. There was a significant treatment-by-time interaction indicating a significantly greater reduction in repetitive behaviors across time for fluoxetine than for placebo. With respect to overall improvement, there were significantly more responders (defined as a Clinical

Global Impression score of <2) at week 12 in the fluoxetine group than in the placebo group. Fluoxetine and norfluoxetine blood levels did not significantly correlate with response. Treatment was generally well tolerated; treatment-emergent side effects included usual SSRI side effects such as vivid dreams and mild insomnia. This is the first randomized placebo-controlled trial of fluoxetine in adults with ASDs. Study limitations include a small sample size, lack of long-term data, and lack of neuroimaging or genetics data. Nevertheless, in the setting of a recent large negative study of citalopram in children with ASDs, this positive study of moderate-to-high dose fluoxetine supports earlier studies suggesting efficacy of SSRIs for the core features of ASDs and supports continued evaluation of drug- and subject-related factors that may be associated with response and side effects in this growing patient population.

– Written by Jonathan E Alpert

Phillips JL, Batten LA, Aldosary F, Tremblay P, Blier P. Brain-volume increase with sustained remission in patients with treatment-resistant unipolar depression. *J. Clin. Psychiatry* doi:10.4088/JCP.11m06865 (2012) (Epub ahead of print).

Cross-sectional MRI studies of individuals with major depressive disorder have found brain volume reductions in frontal, limbic and striatal regions compared with healthy controls. These studies have generated interest in a putative role for stress-induced reductions in levels of brain-derived neurotrophic factor in the pathophysiology of volume loss in depression and have contributed to hypotheses regarding the potential relevance of antidepressants, which increase brain-derived neurotrophic factor expression for protection against volume loss. Neuroimaging studies have shown less volume loss for individuals, whose depression remitted, than in nonremitters, although these studies were not designed to separate out the impact of treatment from that of remission. This prospective observational

cohort study investigated the role of remission in lessening brain atrophy in depression in a small cohort receiving active pharmacotherapy for treatment-resistant depression. Baseline MRI scans were obtained from 27 patients with a history of treatment-resistant depression at baseline and at follow-up after either 6 months of sustained remission (Montgomery–Asberg Depression Rating Scale score ≤ 12 ; $n = 15$) or 12 months of failure to remit ($n = 12$). All subjects received intensive pharmacotherapy, typically involving a combination of pharmacological strategies, under the care of study investigators. In contrast to nonremitters, remitted patients demonstrated a significant mean increase in whole-brain volume during follow-up ($F[1,27]: 9.51$; $p = 0.005$). Within-subject voxel-based morphometry analyses identified increased gray matter volume in remitters in the right orbitofrontal cortex ($t(11): 7.61$; $p = 0.006$) and the right inferior temporal gyrus ($t(11): 6.65$; $p = 0.004$). Nonremitters showed decreased white-matter volume in the left anterior limb of the internal capsule ($t(13): 3.86$; $p = 0.04$). As all subjects received antidepressants, the findings suggest that pharmacotherapy in the absence of sustained clinical remission may be insufficient to elicit volumetric recovery in treatment-resistant depression. Study limitations include a small sample size as well as the use of naturalistic, individualized treatment which precluded inferences regarding the impact of particular drug classes or combinations and regarding treatment–remission interactions. In addition, a region-of-interest approach compared with voxel-based morphometry may have provided more power to detect changes particularly in small structures such as the hippocampus. Finally, the study demonstrates correlation only. Inferences about possible causal relationships between remission and volumetric recovery must be made with care. Nevertheless this study suggests that depressive remission *per se* may have an association with brain volume that is independent from the effects of antidepressants.

– Written by Jonathan E Alpert

Howard R, McShane R, Lindesay J et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N. Engl. J. Med.* 366(10), 893–903 (2012).

There is little data informing prescribing practices for community-dwelling seniors taking anticholinergic medications whose cognition is deteriorating. In this British, multisite, randomized controlled trial of community-dwelling people with probable Alzheimer's disease already receiving donepezil, Howard and colleagues investigate the effect of donepezil and/or memantine treatment compared with placebo on cognitive and functional outcomes. Subjects included adults with probable or possible moderate or severe Alzheimer's disease who had been prescribed donepezil for 3 months or more, had a score of 5–13 on the Standardized Mini-Mental State Examination (SMMSE) and whose doctor was considering a medication change based on existing clinical guidelines. Study subjects were randomized to:

- Active donepezil and placebo memantine
- Active donepezil and active memantine
- Placebo donepezil and active memantine
- Placebo donepezil and placebo memantine

The primary outcomes were week-52 changes in cognition as measured by the SMMSE and changes in functional status as measured by the Bristol Activities of Daily Living Scale (BADLS).

Two hundred and ninety five subjects were randomized, with 73–76 subjects assigned to each arm. However, over the course of the study, 39 subjects died, 37 subjects withdrew, one subject was lost to follow-up and 114 were excluded due to poor adherence with their assigned treatment. 172 subjects were included in the analysis, with 29–51 subjects remaining in each arm. The investigators found that continuing donepezil was associated with a statistically significant reduction in cognitive and functional decline compared with discontinuing donepezil (overall SMMSE difference of 1.9 points with 95% CI: 1.3–2.5 and overall BADLS differences of -3.0 with 95% CI: -4.3 to -1.8), but only the

cognitive benefits reached their predetermined threshold for clinical significance. Similarly, they found memantine to confer statistically significant reductions in cognitive and functional decline compared with placebo (overall SMMSE difference of 1.2 points with 95% CI: 0.6–1.8 and overall BADLS differences of -1.5 with 95% CI: -2.8 to -0.3), although in this case neither reached clinical significance. Combined treatment with donepezil and memantine was not superior to donepezil monotherapy in either measure.

These data offer modest evidence for continuing donepezil in the setting of disease progression in community-dwelling seniors with Alzheimer's disease. Given these modest gains, a follow-up cost-benefit analysis may also be useful in informing clinicians' prescribing practices in this population.

– Written by Jonathan Amiel

Seal KH, Shi Y, Cohen G et al. Association of mental health disorders with prescription opioids and high-risk opioid use in US veterans of Iraq and Afghanistan. *JAMA* 307(9), 940–947 (2012).

Clinicians treating veterans of the wars in Iraq and Afghanistan for mental health disorders including post-traumatic stress disorder (PTSD) with comorbid pain disorders have little data regarding the association between these diagnoses, patterns of prescription opioid use and clinical outcomes. In this retrospective cohort study using the Veterans Affairs (VA) national database, Seal and colleagues search for correlations between PTSD, high-risk opioid use and adverse clinical outcomes. Subjects included veterans of Operation Enduring Freedom and Operation Iraqi Freedom who entered VA healthcare between late 2005 and the end of 2008, and who received a new diagnosis of non-cancer pain within 1 year of commencing care at the VA. The investigators followed identified cases for 1 year following initial pain diagnosis and quantified opioid use by dosage, duration and polypharmacy with other opioids or with sedative hypnotics.

They also tracked adverse clinical outcomes diagnosed in acute care settings including accidents (resulting in injuries, related to opioid use or related to other substance use), self-inflicted injuries and violence.

Of the 291,205 veterans who entered VA care in the study period, 141,029 (48.4%) received a new noncancer pain diagnosis within 1 year of entry. Of these, 15,676 (11.1%) were prescribed opioids. In a subgroup analysis, the authors found that 6.5% of veterans without mental health disorders received opioids, compared with 11.7% with non-PTSD mental health disorders and 17.8% with PTSD. Veterans with PTSD who received prescriptions for opioids were more likely to receive higher doses (adjusted relative risk [RR]: 1.42; 95% CI: 1.31–1.54), opioid polypharmacy (RR: 1.87; 95% CI: 1.70–2.06), sedative-hypnotic polypharmacy (RR: 5.46; 95% CI: 4.91–6.07) and early opioid refills (RR: 1.64; 95% CI: 1.53–1.75). Veterans receiving prescription opioids were more likely to experience adverse clinical outcomes than those who did not receive prescription opioids (RR: 2.33; 95% CI: 2.20–2.46), particularly when they had PTSD.

This study demonstrates that veterans returning from war have a high incidence of pain disorders and those whose pain disorders are comorbid with mental health disorders including PTSD and are prescribed opioids have more risk factors for opioid abuse and are at higher risk for injury than peers without mental health disorders. The retrospective design of the study does not permit inference of causality, but the data do suggest close follow-up of this at-risk population.

– Written by Jonathan Amiel

Bolton PT, Golding J, Emond A, Steer CD. Autism spectrum disorder and autistic traits in the Avon Longitudinal Study of Parents and Children: precursors and early signs. *J. Am. Acad. Child Psychiatry* 51(3), 249–260 (2012).

This prospective longitudinal cohort study examined whether there were identifiable

early signs and precursors of autism spectrum disorder (ASD) within the first 30 months of development. The results have the potential to influence early intervention and screening programs. A total of 13,971 surviving offspring of pregnant women from southwestern England were studied between April 1991 and December 1992. The identification of ASD cases was based on reports from community pediatric records or the special educational needs database from the region. Eighty six children were identified by the age of 11 years. Cases may have been missed as the sample was not systematically screened.

Differences in social and motor development were evident by 6 months of age. At the age 6 months suspected vision problems and the child's ability to say 'mama' or 'dada' were the main predictors of later ASD. By 15 months, concerns regarding hearing and differences in feeding behavior became apparent. By 18 months of age, repetitive behaviors, concerns regarding hearing and health, motor, social, listening, communication and play behaviors were evident. By 24 months of age differences in temperament emerged. By 30 months, increased crying as well as varied bowel habits and stool characteristics developed.

After taking into account full-scale IQ, fewer items remained significant. Those that remained significant included concerns over vision and the ability to understand words (15 months), health concerns (18 months), feeding difficulties and fads (24 months), repetitive and unusual

behaviors (18 and 30 months), and concerns over hearing/ear problems, tempers, as well as social skills (30 months).

– Written by Joan Daughton

Croarkin PE, Wall CA, Nakonezny PA et al. Increased cortical excitability with prefrontal high-frequency repetitive transcranial magnetic stimulation in adolescents with treatment-resistant major depressive disorder. *J. Child Adolesc. Psychopharmacol.* 22(1), 56–64 (2012).

In 2008, the US FDA approved transcranial magnetic stimulation (TMS) as a treatment for major depressive disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode. This study examined the changes in motor cortical excitability in adolescent subjects receiving open label, high-frequency prefrontal repetitive TMS (rTMS). All subjects had failed to adequately respond to two adequate antidepressant trials of at least 6 weeks. All subjects continued treatment with a stable dose of a serotonin-selective reuptake inhibitor and were allowed to continue previously prescribed sleep aids.

The treatment course consisted of 30 sessions given 5 days per week over 6–8 weeks. The study sample included seven females and one male with an

average age of 16.1 years. The average length of the current depressive episode was 20.4 months and the mean Children's Depression Rating Scale–Revised total score at baseline was 69.3. One subject dropped out of the study due to scalp discomfort. Limitations of this study include the small sample size and no control group.

This data suggest that high-frequency rTMS delivered to the left dorsolateral prefrontal cortex of adolescents with treatment-refractory major depressive disorder may increase motor cortical excitability. It is postulated that this is correlated with long-term potentiation. It is also important to point out that increased cortical excitability can increase the risk for seizures and this should be monitored. This is congruent with some adult TMS and neuroimaging research. Further work with measures of cortical excitability and inhibition could aid in the classification of illness severity or prediction of response to treatments.

– Written by Joan Daughton

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