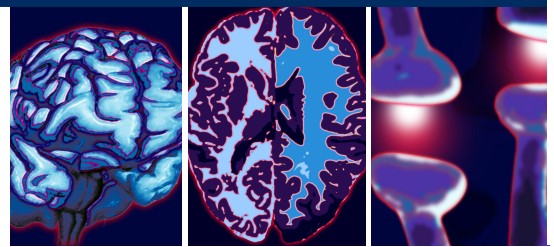


JOURNAL WATCH



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

Expert: Jonathan E Alpert, Harvard Medical School, MA, USA

James LM, Engdahl BE, Leuthold AC, Lewis SM, van Kampen E, Georgopoulos AP. Neural network modulation by trauma as a marker of resilience: differences between veterans with posttraumatic stress disorder and resilient controls. *JAMA Psychiatry* 70(4), 410–418 (2013).

As many as 30% of veterans meet lifetime criteria for post-traumatic stress disorder (PTSD). The prevalence of PTSD among veterans underscores the importance of elucidating the pathophysiology of PTSD, while also identifying the neural mechanisms related to resilience. Resilience is generally conceptualized as the flexibility of psychological and physiological processes in the adaptation to stressors that maintain health and protect against psychopathology in the setting of potentially traumatic events.

In the current study, investigators used magnetoencephalography (MEG) to examine dynamic neural functioning among US veterans diagnosed with PTSD ($n = 86$) compared with non-PTSD veteran controls ($n = 113$). Veterans with other axis I psychiatric diagnoses, traumatic brain injury or other significant CNS disorders were excluded. Local and global neuronal interactions were quantified by studying synchronous neural interactions (SNIs). Consistent with models of resilience emphasizing plasticity, investigators hypothesized that the control, but not PTSD, subjects would exhibit neural flexibility or adaptation to potentially traumatic events, as indicated by modulation of SNIs by these events. Lifetime trauma

exposure, including mainly combat-related events, but also other events such as sexual assault, was assessed with the Deployment Risk and Resilience Inventory.

Global SNIs were significantly modulated downward with increasing lifetime trauma scores in resilient control veterans ($p = 0.003$) but not in veterans with PTSD ($p = 0.91$). This effect, which was primarily characterized by negative slopes ('decorrelations') in small neural networks, was strongest in the right superior temporal gyrus. Significant negative slopes were more common, stronger and observed between sensors at shorter distances than positive slopes in both hemispheres ($p < 0.001$ for all comparisons) for veteran controls, but not for veterans with PTSD. Although the control group reported significantly lower lifetime trauma exposure overall compared with veterans, additional analyses only comparing subjects with similar trauma exposure revealed the same pattern of downward modulation of SNI with trauma in the control group ($p = 0.001$) and not in the PTSD group ($p = 0.60$).

Overall, these findings suggest the possibility that a basic mechanism of adaptation to potentially traumatic events involves decorrelation of neural networks, particularly in the right superior temporal gyrus, an area of interest from prior studies of PTSD. Investigators advance the hypothesis that decorrelation may represent a mechanism by which a network is freed up from the hold of a particular sensory input, such as a potentially traumatic event, and becomes more available for encoding a new experience. Such a mechanism may putatively underlie resilience.

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Limitations of this study include the early stage of MEG research, which prevents more precise conclusions about the relevance of downward modulation of SNIs to the phenomena of psychological and physiological flexibility. In addition, the measure of lifetime exposure to potentially traumatic events in this study did not include the assessment of an actual reaction to those events, another meaningful dimension for evaluating lifetime trauma burden. Finally, PTSD often occurs in the context of significant psychiatric and medical comorbidity, including depression, addiction and traumatic brain injury. Although it is appropriate to have excluded subjects with comorbidity in this preliminary study, the degree to which the findings generalize to the majority of veterans and other individuals presenting for treatment of PTSD remains to be clarified.

Nevertheless, this first study using MEG to study modulation of neural activity by potentially traumatic events in controls as well as individuals with PTSD suggests that further research on decorrelation, generally, and in the area of the superior temporal gyrus, in particular, may offer important leads about neural mechanisms that underlie resilience and may mitigate against the development of PTSD following exposure to trauma.

Andreasen NC, Liu D, Ziebell S, Vora A, Ho BC. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: a prospective longitudinal MRI study. *Am. J. Psychiatry* doi:10.1176/appi.ajp.2013.12050674 (2013) (Epub ahead of print).

Multiple studies have shown smaller mean brain volumes in many regions, particularly the frontal lobes, in individuals with schizophrenia. Current hypotheses emphasize the role of disruption in neurodevelopmental processes, such as gray matter pruning and increased myelination, which normally sculpt the brain into maturity. In addition, however, it has been observed that volume loss continues beyond illness onset, suggesting

the role of other factors. In the current study, investigators focused on the role of recurrent relapses as additional insults that are potentially associated with tissue loss. As relapses often prompt increased antipsychotic medication doses, treatment intensity was also assessed.

In this first study examining the relationship between relapse, treatment and brain tissue loss using quantitative structural MRI in a repeated-measure longitudinal design, the authors analyzed data from 202 patients enrolled in the Iowa Longitudinal Study of first-episode schizophrenia (1987–2007), for whom adequate structural MRI data were available ($n = 659$ scans) from scans obtained at regular intervals over an average of 7 years [1]. Measures of the number of clinically meaningful relapses and duration were taken from the records of follow-up visits conducted at 6-month intervals. Of the 202 subjects, the majority (157) experienced one or more relapses, while 29 had no relapses and 16 had persistent illness of a severity too great to discern relapse and recovery.

Greater relapse duration, although not absolute number of relapses, was associated with total cerebral volume loss with white matter and the frontal lobes particularly affected. However, after adjusting for other effects, antipsychotic treatment intensity was also associated with brain volume changes, including loss of total cerebral volume, total temporal and frontal volume, and parietal white matter volume together with elevated ventricle:brain ratios. These findings highlight a core clinical dilemma. Both relapse and antipsychotic dose escalation typically used to prevent or treat relapse may contribute to the risk of brain volume loss.

Limitations to this study include the correlational and naturalistic nature of the study design precluding definitive conclusions about causality. As the investigators acknowledge, rather than reflecting a consequence of relapse and treatment intensity, progressive brain tissue loss may be a marker for a more severe variant of illness that is associated with both greater relapse duration and treatment refractoriness requiring higher medication doses. While

future studies are needed to identify mechanisms by which relapse and antipsychotic treatment may potentially contribute to brain tissue loss, the preliminary findings of this longitudinal study strongly support the often challenging goals of averting relapse while using the lowest effective medication doses possible, and reinforce the importance of strategies that improve medication adherence while optimizing adjunctive non-medication approaches that support lower antipsychotic dosing.

Reference

- 1 Flaum MA, Andreasen NC, Arndt S. The Iowa Prospective Longitudinal Study of Recent-Onset Psychoses. *Schizophr. Bull.* 18, 481–490 (1992).

Preskorn SH, Kane CP, Lobello K et al. Cytochrome P450 2D6 phenoconversion is common in patients being treated for depression: implications for personalized medicine. *J. Clin. Psychiatry* doi:10.4088/JCP.12m07807 (2013) (Epub ahead of print).

Genotyping related to the hepatic cytochrome P450 2D6 (CYP2D6) isoenzymes that metabolize the majority of clinically used drugs is widely considered an important element in the development of personalized medicine by virtue of the insight it may provide about an individual's metabolism of common medications. Genetic polymorphisms affecting the activity of key enzymes, such as CYP2D6, allow individuals to be classified as poor metabolizers, intermediate metabolizers, extensive metabolizers or ultrarapid metabolizers of substrates that rely on this particular enzyme for metabolism based on the combination of alleles they carry. This status, in turn, has significance for drug tolerability and efficacy. Notable examples, such as tamoxifen and certain opioids, require conversion by CYP2D6 to an active drug. These agents are found in higher concentrations among poor CYP2D6 metabolizers but are markedly less effective by virtue of lower levels of the active metabolite.

Nevertheless, while genotyping may guide drug selection and dosing decisions to some extent, individuals with a non-poor metabolizer genotype may, in fact, be converted to a poor metabolizer phenotype by virtue of concomitant medications (e.g., paroxetine) that inhibit CYP metabolism. For this reason genotyping may underestimate the true prevalence of the poor metabolizer phenotype.

In this first large-scale antidepressant study to assess the incidence of phenocconversion to CYP2D6 poor metabolizer status in clinical practice, investigators studied 900 depressed subjects (≥ 18 years) receiving venlafaxine extended-release (37.5–225 mg/day) for up to 8 weeks at 50 study sites. A 15-ml blood sample was drawn 4–12 h after the patients' last antidepressant dose. Plasma *O*-desmethylvenlafaxine and venlafaxine concentrations were determined for each patient. A CYP2D6 poor metabolizer phenotype was defined, according to standardized guidelines, as an *O*-desmethylvenlafaxine to venlafaxine ratio of < 1 . CYP2D6 genotype was also determined for each patient.

Of the total sample, only 4% (35) of subjects were genotypic CYP2D6 poor metabolizers. However, the incidence of the CYP2D6 poor metabolizer phenotype, as determined by an *O*-desmethylvenlafaxine to venlafaxine ratio < 1 , was nearly sevenfold greater (27%; 243 subjects). Based on known racial and ethnic influences on CYP genotypes, a subanalysis was undertaken, which showed an anticipated difference in poor metabolizer status between African-American (0.9%) and white (4.4%) subjects when based on genotype, and a significant increase in poor metabolizer status in both African-American (22.2%) and white (27.2%) subjects when based on phenotype.

Similar to other clinical populations, over three-quarters of subjects were taking medications other than the studied antidepressant. As expected, conversion to the poor metabolizer phenotype was significantly more common among individuals taking known CYP2D6 substrates or inhibitors (40%) than among those not taking those agents (13%; $p < 0.001$). The

report does not provide data to explain the lack of concordance between genotypic and phenotypic CYP 2D6 status among subjects not on CYP 2D6 substrates or inhibitors.

Overall these results exemplify the significant limitation of CYP genotyping for estimating true functional metabolic capacity of patients who are on multiple medications. Although the study does not evaluate the clinical relevance of phenocconversion, previous work by this group suggests that phenotypic CYP2D6 poor metabolizers respond less well to venlafaxine among phenotypic CYP2D6 presumably because efficacy relies, in part, upon the *O*-desmethylvenlafaxine metabolite [1] produced by CYP2D6. In summary, while genotyping may play a role in the future of personalized pharmacotherapy, for some isoenzymes such as CYP2D6 genotyping will seriously underestimate the prevalence of poor metabolizer functional status and may, therefore, not accurately predict tolerability and efficacy particularly among individuals on multiple medications.

Reference

- 1 Lobello KW, Preskorn SH, Guico-Pabia CJ *et al*. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. *J. Clin. Psychiatry* 7(11), 1482–1487 (2010).

Schlaepfer TE, Bewernick BH, Kayser S, Mädler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biol. Psychiatry* doi:10.1016/j.biopsych.2013.01.034 (2013) (Epub ahead of print).

A majority of individuals with major depressive disorder fail to remit during their first antidepressant treatment trial. As many as a third fail to remit despite multiple sequential trials, as well as antidepressant augmentation and combination treatments. For individuals with exceptionally resistant depression, small clinical series of deep-brain stimulation (DBS) have produced promising results

focusing on three different target areas for stimulation: the subgenual cingulate gyrus, anterior limb of the capsula interna and nucleus accumbens. However, even in these positive series, response rates were in the range of 50–60% and remission rates considerably lower.

Components of brain reward circuitry that have been implicated in depression include the nucleus accumbens, ventral tegmental area, ventromedial and lateral hypothalamic nuclei, and the amygdala, which are interconnected through the medial forebrain bundle. In this pilot study, investigators assessed the safety and efficacy of DBS to the superolateral branch of the medial forebrain bundle in seven adults with severe recurrent and/or chronic depression who had failed to respond to at least three adequate trials of an antidepressant, two adequate trials of augmentation/combination treatment, an adequate trial of electroconvulsive therapy (≥ 6 bilateral treatments) and more than 20 sessions of individual psychotherapy. All subjects had unipolar depression with the exception of one patient with bipolar disorder whose last manic episode occurred 23 years before the study. Target stimulation sites were identified by individual deterministic diffusion tensor imaging.

Six of the seven patients had a reduction in depressive symptoms by day 2 of stimulation. Four patients met the criteria for a response (reduction of the Montgomery-Åsberg Depression Rating Scale [MADRS] by $> 50\%$) by day 7, five met the criteria for a response by week 6 and six met the criteria for a response by last observation (12–33 weeks), with four showing symptom remission (MADRS < 10). Adverse events included dose-related strabismus and dizziness, a small intracranial bleed during surgery and infection at the implanted pulse generator site. Dose escalation was primarily limited by oculomotor effects and the mean current (2.86 mA) was generally lower than in previous DBS studies.

Limitations of the study include its small sample size, the absence of a sham control and the relatively short duration of follow-up. In addition, most patients continued

on other treatments, so conclusions cannot be drawn about DBS as a monotherapy. Nonetheless, this preliminary study suggests that rapid onset and potentially enduring antidepressant effects can be produced among patients with markedly refractory depression using a relatively low current through stimulation of the

superolateral branch of the medial fore-brain bundle, an area of particular interest with respect to the relationship between depression and brain reward pathways.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a

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

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