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Schneiderian First-Rank Symptoms and Right Parietal Hyperactivation: A Replication Using fMRI

TO THE EDITOR: Schneiderian first-rank symptoms of schizophrenia may reflect defective "internal monitoring" of intentions and actions by aberrant sensory systems. Previous positron emission tomography (PET) studies have implicated right parietal hyperactivation (Brodmann's area 40) (1, 2). The latter may arise from a failure of "forward-modeling" so that endogenous sensory data (consequent upon voluntary motor activity) are felt to originate outside the subject (3, 4). Failure to predict the sensory consequences of actions might be associated with failure to attenuate sensory-related neural activity; hence, the parietal hyperactivation observed with PET (1–4).

Using an event-related functional magnetic resonance imaging (fMRI) paradigm, permitting subjects to choose the timing of their own movements, we examined the hypothesis that patients experiencing first-rank symptoms exhibit hyperactivation of right Brodmann's area 40 (compared to patients without first-rank symptoms). Also, consistent with the "forward-modeling" hypothesis, we predicted that aberrant right Brodmann's area 40 activation would follow that of the primary motor cortex (Brodmann's area 4).

Functional imaging data were acquired on a 1.5-T system in 13 right-handed, male schizophrenia (DSM-IV) patients, each studied twice, with written informed consent and ethics committee approval. Patients with first-rank symptoms (N=7) (age: mean=36 years, SD=11; illness duration: mean=15 years, SD=11; premorbid IQ: mean=102.1, SD=9.7; chlorpromazine equivalents: mean=507.1 mg/day, SD=255.7; extrapyramidal symptom score: mean=5.6, SD=10.5) were comparable with those without first-rank symptoms (N=6) (independent-sample t test, df=11, p>0.05 on all measures). The patients performed spontaneous, freely timed movements using their right index finger in an event-related fMRI paradigm (5). Images were analyzed by using a random-effects model in statistical parametric mapping. The validity of the parametric results was examined with nonparametric permutation tests. We examined the response latency in left Brodmann's area 4 and right Brodmann's area 40 by using time to half-maximum blood-oxygen-level-dependent response as a measure of latency (5).

Statistical parametric mapping analysis revealed that patients with first-rank symptoms had significant hyperactivation of right Brodmann's area 40 (Talairach coordinates=57, –29, 36) (t=4.7, df=24, uncorrected p<0.0001, two-sample t test; family-wise error corrected: p<0.02 [volume-of-interest right Brodmann's area 40]) relative to patients without first-rank symptoms. A two-group test (5,000 permutations) in statistical parametric mapping supported the validity of this finding (t=4.7, df=24, p=0.0002). Mean time to half-maximum response was 177 msec later in right Brodmann's area 40 than left Brodmann's area 4.

To our knowledge, this is the first fMRI study replicating previous PET findings with regard to first-rank symptoms (1, 2). Of importance, the observations derive from an ecologically valid spontaneous movement paradigm (approximating "truly" spontaneous behavior, as might occur outside the scanner [5]). The observation that parietal cortex activation occurs later than that of motor cortex supports the "forward-modeling" hypothesis.

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Antidepressants for Bipolar Depression

TO THE EDITOR: Meta-analysis represents an "observational study of studies." The benefits of random assignment and the removal of confounding bias within a sample are lost with meta-analysis, resulting in the problem of "heterogeneity" between study samples. Just as randomized clinical trials are more valid than observational studies, a meta-analysis of one to five randomized clinical trials is not necessarily more valid than one well-designed randomized clinical trial. This issue may be less relevant if studies agree, as it appears they did in the meta-analysis by Harm J. Gijsman, Ph.D., M.R.C.Psych., et al. (1). However, this apparent agreement hides important unexplored heterogeneity, which does not invalidate the meta-analysis but can lead to its misinterpretation.

For instance, the only placebo-controlled study that found no evidence of acute antidepressant response is the only study, to our knowledge (2), in which all patients received baseline lithium. Among other studies, one (3) nonrandomly assigned 37% of the patients in the antidepressant arm to lithium versus 21% in the placebo arm—a relative 77% increased lithium use in the antidepressant arm—hardly a fair assessment of fluoxetine versus placebo. Two compared antidepressant alone to placebo alone, and one large study (58.5% of all meta-analysis patients) (4) compared olanzapine plus fluoxetine to olanzapine alone ("placebo" improperly referred to olanzapine plus placebo). These studies may suggest acute antidepressant efficacy compared to no treatment or olanzapine alone but not compared to the most proven mood stabilizer, lithium, which is also the most relevant clinical issue.

Regarding antidepressant-induced mania, two studies comparing antidepressants without mood stabilizer to no treatment (placebo only) reported no mania in any patients: an oddity, if true, since it would suggest that even spontaneous mania did not occur while those patients were studied or that perhaps manic symptoms were not adequately assessed. As described, another study preferentially prescribed lithium more in the antidepressant group (3), providing possibly unequal protection against mania. Although the olanzapine-fluoxetine data suggest no evidence of switching while using antipsychotics, in our reanalysis of the lithium-plus-paroxetine (or imipramine) study, there was a threefold higher manic switching rate with imipramine versus placebo (risk ratio= 3.14), with asymmetrically positively skewed confidence intervals (0.34–29.0). Combined with other studies reviewed that showed higher tricyclic antidepressant switching rates than other antidepressants, attention to this heterogeneity suggests that one cannot rule out antidepressant switching.

Finally, these short-term (up to 10 weeks) studies are only relevant, if at all, to the acute depressive episode. Contrary to the highly selective review in the discussion, they do not provide any evidence to support long-term maintenance use of antidepressants in bipolar disorder, which was previously shown ineffective in multiple randomized clinical trials in a systematic review (5).

In summary, our critique touches partly on the validity of this meta-analysis, but more importantly, on its generalizability due to unexplored heterogeneity. Apparent agreement among studies hides major conflicting results between the only adequately designed study using the most proven mood stabilizer, lithium, and the rest. It would appear that the rosy conclusions of the meta-analysis are premature when the clinical options involve use of proven mood stabilizers, such as lithium, with or without antidepressants.

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TO THE EDITOR: The review of antidepressants for bipolar depression by Dr. Gijsman et al. provided an excellent overview of the randomized, controlled trials in the literature. However, the presented data all reflect acute antidepressant treatment response, with the longest study duration (10 weeks). Bipolar disorder is a chronic, relapsing condition, with an etiology likely distinct from that of unipolar depressive disorder, for which current antidepressants were specifically developed. Treatment approaches applied to alleviate symptoms during acute exacerbations may have significant impact on the long-term course of the illness. The authors did not present evidence that the long-term outcomes are favorable with antidepressant treatment; thus, their conclusion to challenge the APA practice guideline for recommending lithium or lamotrigine as first-line treatment for bipolar depression is unfounded.

There are long-term (of 11–24 months) prospective, placebo-controlled (1–3), naturalistic prospective (4, 5), and retrospective studies (6)—excluded categorically from the current review—showing that antidepressant exposure is associated with worse long-term outcomes in patients with bipolar disorder, apart from the concern for acute mania. Developing treatment guidelines requires an integration of all available data.

The question of whether bipolar depression responds best to adding a mood stabilizer or an antidepressant may be amenable to investigation by a long-term practical clinical trial. This model of structuring studies to compare relevant alternative interventions in diverse, real-life patient populations and practice settings is gaining support from research decision makers. Current data on antidepressants in bipolar depression do not justify changing the APA treatment guidelines.

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TO THE EDITOR: The conclusion of a recently published review and meta-analysis by Dr. Gijsman et al. of antidepressant