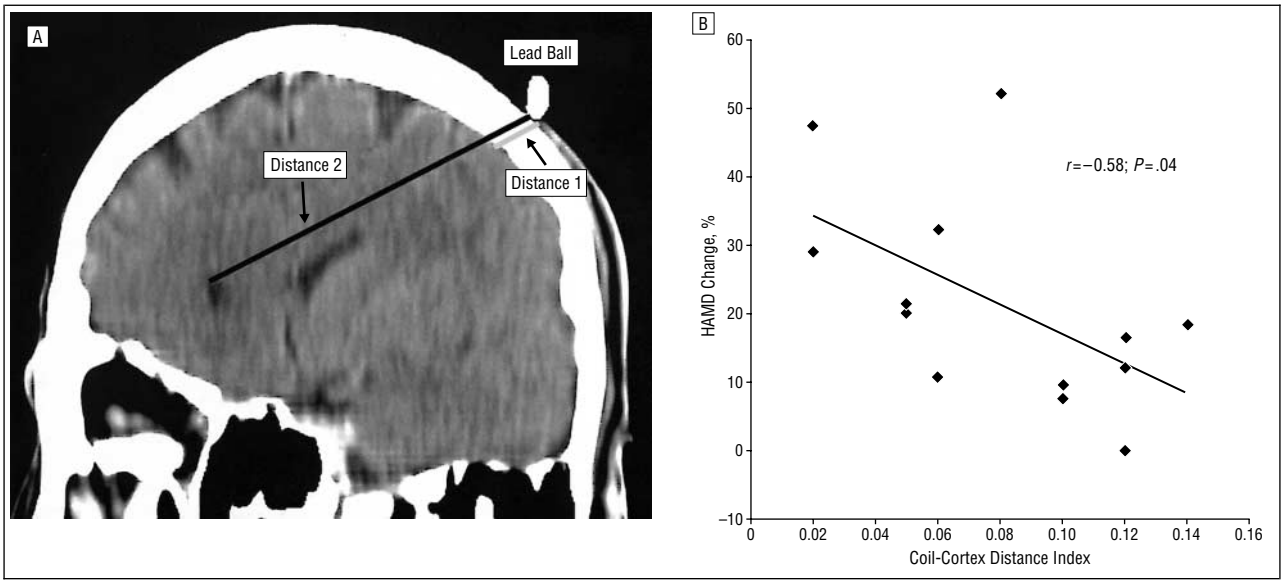
Antidepressant Effects of Repetitive Transcranial Magnetic Stimulation in the Elderly: Correlation Between Effect Size and Coil-Cortex Distance

Several controlled studies suggest that high-frequency repetitive transcranial magnetic stimulation is associated with antidepressant effects.[1-5] Interestingly enough, the 2 studies investigating relatively older depressed patients[2,5] demonstrated a lesser effect than did the studies performed in a younger population. This is in stark contrast to the finding that another method of brain stimulation, electroconvulsive therapy, is somewhat more effective in older patients.[6] Figiel et al[2] assumed that this finding could be associated with the structural brain changes that are often found in older depressed patients.[7] Lai and colleagues[8] were recently able to demonstrate an orbitofrontal cortex volume reduction in geriatric depressed patients. Kozel et al[9] investigated the relationship of the distance between the stimulating coil and the cortex to age and antidepressant response and were not able to find a significant correlation in 12 patients with a mean age of 42 years; however, they demonstrated that treatment responders were younger and had a shorter prefrontal coil-cortex distance.

To investigate the hypothesis that a relative prefrontal atrophy could be related to the antidepressant response, we assessed the correlation between an index of the distance between the stimulating coil and the cerebral cortex (coil-cortex distance index [CCDI]) and the rate of change in Hamilton Depression Scale (HAMD) rating[10] in 13 relatively older outpatients (mean±SD age, 56.4±12.7 years; range, 40-74 years) with treatment-resistant major depression. This index was the difference of the coil-cortex distance at the prefrontal stimulation site minus the coil-cortex distance at the site where motor threshold was assessed, the result representing relative prefrontal atrophy. The patients underwent a standard repetitive transcranial magnetic stimulation treatment protocol. Stimulations were performed with a high-speed stimulator (Magstim Company Ltd, Whitland, Wales) with a figure 8–shaped air-cooled coil applied to the left dorsolateral prefrontal cortex (DLPFC), as described in other studies.[11] Stimulus intensity was 100% of individual motor threshold at a frequency of 20 Hz. The duration of the stimulus train was 2 seconds and the intertrain interval was 28 seconds. Forty trains were applied in 20 minutes (1600 pulses) during each session, and sessions were repeated every day for 2 weeks.

Brain measurements to obtain the CCDI were performed using computed tomography with a multislice spiral computed tomographic scanner (Somatom +4 Volume Zoom; Siemens AG, Munich, Germany). The stimulation sites for motor cortex and DLPFC were marked with lead balls fixed to a swim cap that was individually fitted for each patient. The position of the cervical spine in the scanner was the same as in the stimulation chair (reclined 15°). Overlapping 5-mm axial slices (increment, 1 mm) were reconstructed in the axial planes. Distances for motor cortex and left DLPFC stimulation



A, A ratio of the distance from the stimulating coil (marked with a lead ball to the surface of the cortex [distance 1] and another from the coil to the contralateral side ventricle [distance 2], used as a proxy for total brain volume) was obtained at the motor cortex and at the dorsolateral prefrontal cortex (DLPFC). The coil-cortex distance index is the difference between the ratio at the prefrontal cortex and the one at the DLPFC, thus taking into account a putative disproportionate atrophy of the cortices. B, Graphic illustration of a significant correlation of this index with the decrease in depression rating as assessed with the Hamilton Depression Scale (HAMD).

were measured in the respective axial planes, defined by a lead ball at the position of stimulation and the apex of the anterior knee of the contralateral side ventricle (**Figure**, A). The CCDI was defined as the difference between the ratio of a distance 1 (measured from the skull surface to the surface of the brain parenchyma) and a second distance 2 (measured from the skull surface to the apex of the anterior knee of the contralateral side ventricle) at both the motor threshold and DLPFC stimulation sites (Figure, A). This ratio was calculated to correct for individual differences in brain size, taking distance 2 as a proxy measurement for brain size. Since the action of the magnetic field on the brain is determined by both distance and volume of the brain, we considered it important to correct for individual volume differences.

The patients showed an improvement in HAMD rating (mean±SD reduction, 21.2%±18.0%, $P<.001$). The intraclass correlation[12] between CCDI measurements of 2 independent blinded raters (U.P.M. and T.E.S.) was high (intraclass correlation=0.89; F=18.33; $P<.001$). We found no correlation between the distances at the stimulation site, the distances at the motor cortex, and age and the severity of the depression. However, a negative correlation was found between the CCDI and the percentage of the HAMD rating decrease before and after treatment (Pearson correlation, 2-tailed: $r=-0.58$; $P=.04$, Figure, B), indicating that this difference between the prefrontal and motor cortex coil-cortex distances is correlated with antidepressant response as hypothesized. Our study demonstrates that there might indeed be a process of prefrontal atrophy that outpaces motor cortex atrophy in chronically depressed middle-aged subjects. This finding is important in explaining the neurobiology of depression in an older patient population and in designing future repetitive transcranial magnetic stimulation treatment studies in this very important patient group.

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Did Ezekiel Have Temporal Lobe Epilepsy?

In addition to intrinsic, historical, and literary interest, the study of the history of a disease can have pedagogical and even clinical utility by providing memorable exemplar cases. I point out what might be the oldest known case (approximately 2600 years ago) of temporal lobe epilepsy (TLE)[1,2]: the biblical figure Ezekiel, son of Buzi.[3] Appreciation that Ezekiel may have had TLE might be an aid in understanding the Book of Ezekiel, which has proved largely inscrutable to previous religious, literary, and historical study.[4]

The Book of Ezekiel consists of Ezekiel's prophecies from the years 593 to 577 BC.[4] These years include the fall of Jerusalem and the destruction of Solomon's Temple in 586. There is not much biographic information available for Ezekiel, but he is known to have come from a priestly family (Ezekiel 1:3) and thought to be a descendant of the Chief Priest Zadok.[4] Chapters 1 to 24 of the Book of Ezekiel contain Ezekiel's prophecies against Israel and Judah; chapters 25 to 32, oracles against foreign nations; and chapters 33 to 48, oracles about the future glory of Israel.

In 1975 in these ARCHIVES, Waxman and Geschwind[1] noted in some patients with TLE a constellation of signs and symptoms—hyperreligiosity, hypergraphia, and altered sexual behavior—during interictal periods. Other signs of this "Geschwind syndrome" can include aggression, pedantic speech, circumstantiality or a "sticky" personality, and psychosis.[2] Many patients with TLE do not demonstrate this flagrant "temporal lobe personality," so absence of neuropsychiatric symptoms does not rule out a diagnosis of TLE, but presence of the signs and symptoms is highly suggestive. The supranormal sign of hypergraphia is potentially of particular utility, as it is not typically seen in other diseases.

As can be discerned from inspection of the text,[3] Ezekiel shows extreme religiosity—concern with the process and inner mechanistic workings of a given religion or religions. Indeed, not only does Ezekiel comment and prophecy on nearly all aspects of the implications of religion for spiritual and daily life, but he is concerned with the minute details of the blueprints of the house of worship (Temple) itself (chapters 40-42).[4] None of the other pious or religious individuals in the Bible show the aggressive religiosity of Ezekiel. The Book of Ezekiel[3] demonstrates repetitive hypergraphia: It is the fourth longest book in the Bible,[3] more than 50% longer than Leviticus, and only 3% shorter than all of Genesis! Although Ezekiel's sexuality is not mentioned, he extensively and in great depth, in a manner typical of patients with TLE, criticizes various women whom he feels are harlots (eg, Ezekiel 16:15 and chapter 23). Ezekiel's prophecies are aggressive and pedantic (see especially chapters 20-24). An archetypal example of pedantry is the following (Ezekiel 20:2-5)[3]:

> Then came the word of the LORD unto me, saying, "Son of man, speak unto the elders of Israel, and say unto them, 'Thus saith the Lord GOD; Are ye come to enquire of me? As I live, saith the Lord GOD, I will not be enquired of by you.' . . . And say unto them, Thus saith the Lord GOD. . . .

Ezekiel has the "sticky" personality of patients with TLE—difficult to get them to leave the office. For example, in chapters 40 to 42, Ezekiel tours the reader around every aspect and angle of the Temple. Ezekiel also demonstrates neurologic symptoms, recognized more than a century ago by a biblical scholar,[5] that are consistent with a diagnosis of epilepsy: multiple episodes of fainting spells (Ezekiel 1:28; 3:23; 43:3; and 44:4) and mutism (Ezekiel 3:22-26; 24:25-27; and 33:21 ff.).

A diagnosis of schizophrenia has been considered[6] but ruled out for Ezekiel (no other specific medical diagnosis was offered). In addition, as one necessary criterion for schizophrenia[7] is greatly diminished social functioning, it seems unlikely that Ezekiel could have kept up his productive ministry for so long with chronic schizophrenia. Also, hypergraphia is typically not seen in schizophrenia. Bipolar disorder would also have to be in the differential diagnosis for Ezekiel. Although no detailed description of his actions are given, thus making it impossible to rule out bipolar disorder, the long-term, sustained nature of Ezekiel's writings make this diagnosis less likely. There is no evidence of alcohol or substance abuse. Migraine might produce some of Ezekiel's neurologic signs but, in isolation, not his hypergraphic writings. There is no evidence of other organic medical disease. Given that Ezekiel demonstrates so many of the neuropsychiatric and neurologic signs and symptoms of TLE, especially in a time when there was no published material describing it, it seems hard to believe that the author of the Book of Ezekiel (Ezekiel or someone else) made up this style of writing without having TLE himself or observing someone who did. The occurrence of TLE thousands of years ago is consistent with current thinking that TLE represents a common final end point for a variety of genetic, prenatal and perinatal, and developmental lesions, perhaps acting in concert, which are also likely to have great antiquity. I hope this note stimulates further interest in study of the Book of Ezekiel and the history of TLE.

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Chorion Type and Twin Similarity for Child Psychiatric Symptoms

Twin studies suggest significant genetic influence on all dimensions of childhood problem behavior measured with the Child Behavior Checklist (CBCL),[1] which may increase with age.[2-5] However, such twin studies have been criticized for assuming that monozygotic (MZ) and dizygotic (DZ) twins have similar prenatal environments.[6-8] Monozygotic twins share the same chorion in most cases (monochorionic [MC]), whereas all DZ, and around a third of all MZ, twins are of the dichorionic (DC) type.[6,9] The importance of these differences lies in the effects they have on placental development. Because the placenta is formed of chorionic tissue, DZ and MZ-DC twins will have separate placentas. Although these placentas may fuse macroscopically, fusion of 2 separate placentas only rarely results in direct vascular anastomoses in human twins,[6,10,11] suggesting that their placentas remain functionally separate. However, MZ-MC twins share the same placenta. This results in competition between the twins for nutrition, which makes them substantially lighter at birth than other twins.[6] In addition, sharing the same placenta may more often result in shared exposure to a prenatal environmental risk factor for psychiatric disorders, resulting in "environmental" concordance.[12-14] Earlier studies

Variance Components and Fit Statistics of Several Models for the CBCL Total Problem Score*

Model	a^2	c^2	d^2	e^2	ch^2	χ^2	AIC	*df*	*P* Value
AE	0.84	. . .	. . .	0.16	. . .	42.76	34.76	4	<.001
CE	. . .	0.72	. . .	0.28	. . .	59.40	51.40	4	<.001
E	. . .	. . .	. . .	1.00	. . .	596.56	586.56	5	<.001
ADE	0.84	. . .	0.00	0.16	. . .	42.78	36.78	3	<.001
ACE	0.41	0.43	. . .	0.17	. . .	2.21	−3.80	3	.53
ACE-Ch	0.41	0.42	. . .	0.16	0.00	4.96	−5.04	5	.42

*CBCL indicates Child Behavior Checklist; AIC, Akaike information criterion; A, additive genetic effects; E, effects of nonshared environment; C, effects of shared environment; D, dominance genetic effects; Ch, chorionicity; a^2, c^2, d^2, e^2, ch^2, proportion of variance; and ellipses, data not applicable.

suggested higher concordance rates for schizophrenia[15] and less intrapair differences for poor self-control, social incompetence, and internalizing symptoms[16] in MC than in DC co-twins.

On the other hand, the occurrence of the twin transfusion syndrome in MZ-MC twins may result in greater within-pair variability for a range of birth outcomes that could influence subsequent mental health and, thus, contribute to a greater degree of discordance for childhood psychiatric symptoms in MZ-MC twins.

If twin studies do not consider differences in prenatal environment occasioned by chorionicity, too much causal influence could be attributed to either genetic or environmental factors. Because childhood psychiatric symptoms are a risk factor for adult psychiatric outcomes,[17,18] adult heritability estimates could be similarly confounded.

Subjects and Methods. *Subjects.* The East Flanders Prospective Twin Survey collects information, since 1964, on the mother, the placenta, and the child in 98% of multiple births in East Flanders, Belgium. At present, the register counts more than 5600 twin pairs.[19] Zygosity and chorionicity are determined by examination of fetal membranes, blood groups, and, since 1982, 5 highly polymorphic DNA markers.[20] The probability of zygosity in same-sex DC pairs is calculated by sequential analysis.[20] To be included in the analysis, all the DC-MZ pairs had to reach a probability of monozygosity of at least 95%. Twins aged 6 to 17 years were selected for the present study. Questionnaires were sent to the 1436 parents of these twin pairs, of which 760 returned the questionnaires. Of these 760, 425 were DZ (217 same-sex and 208 opposite sex pairs), 125 were MZ-DC, and 202 were MZ-MC. Six pairs with major congenital malformations were excluded, as were 2 pairs with unknown zygosity and an implausible registered birth weight.

Measures. Parents gave written informed consent and completed the CBCL.[21] This questionnaire measures the extent to which children have behavioral and emotional problems as seen by the parents. Although the CBCL allows for the calculation of 8 separate scores corresponding to several behavioral dimensions, large-scale population studies[22] show inadequate empirical support for these syndromes and their differentiation. Instead, a general problem behavior factor seems to underlie CBCL data across different age groups.[22,23] We, therefore, examined the total amount of psychiatric symptoms, as measured by the total problem score, subjected to a square root transformation to achieve normality.

Statistical Analyses. Structural equation modelling was used to fit theoretically motivated models to the CBCL data.[24,25] Twin models of psychiatric symptoms usually assume an effect of 4 latent variables on observed phenotypic variance: additive genetic effects (A), dominance genetic effects (D), effects of shared environment (C), and effects of nonshared environment (E). Model fitting is used to determine which model best fits the data. Models assuming influences of different latent variables, such as AE, ACE, or ADE models, are compared with each other to determine which one represents the best compromise between goodness of fit (using model χ^2 values) and parsimony (using some information criterion, such as the Akaike information criterion[24,26]). The relationship between the latent variables and the observed data is usually examined in 2 populations: MZ and DZ twins. In the present study, 3 populations were used: MZ-MC, MZ-DC, and DZ twins. In addition, we added a fifth latent variable, Ch, representing chorionicity, which was shared between MZ-MC twins (correlation, 1) and not shared between MZ-DC and DZ twins (correlation, 0).

Results. The correlation for CBCL scores was 0.64 in DZ pairs, 0.82 in MZ-DC pairs, and 0.83 in MZ-MC pairs. The AE model in the **Table** assumes that the variance consists of only 2 factors: the additive genetic (A) and the nonshared environmental (E) factors. This model had a low goodness of fit ($P<.001$). The models CE, E, and ADE could be rejected as well. The fifth model included the additive genetic factor (A), the shared environmental factor (C), and the nonshared environmental factor (E). The goodness of fit of this model was high ($P=.53$). When the factor chorionicity (Ch) was added to the ACE model, the χ^2 value did not significantly worsen, but this factor did not contribute anything to the variance of the total CBCL problem score (Table). Therefore, the ACE model was the best compromise between goodness of fit and parsimony, as indicated by the smallest Akaike information criterion. Splitting up the sample into twins younger and older than the median age revealed similar results for both groups.

Comment. Previous work in much smaller samples suggests that chorionicity does not affect measures of temperament and cognition in children,[9] although it may possibly influence some dimensions of personality.[9,16] The present results suggest that chorionicity is not a con-

founding factor in twin studies of childhood psychiatric symptoms using the CBCL, and that causal influence may be rightly distributed over environmental and genetic factors. Inasmuch as childhood psychiatric symptoms are a risk factor for adult psychopathological outcomes,[17,18] similar unconfounded environmental and genetic effects on risk can be postulated.

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Samson Was Heroic, Exhausted, Depressed, and in Love, but He Does Not Have Antisocial Personality Disorder

The 6 criteria for antisocial personality disorder (ASPD) that Altschuler and his colleagues suggest[1] for Samson requires a more careful reading of the biblical text, Judges 13 through 16. The following will provide such.

1. It is not generally accepted that social norms will be conformed to in wartime. Samson is at war, as is almost everyone in the book of Judges. The burning of enemy fields and food stocks is a skillful act of the guerrilla fighter that is described as a military tactic in the writings of the ancient historians Herodotus and Livy.

2. Samson is not deceitful to his parents. He does not tell them about the lion, which he has killed, because he neither wished to trouble them with concern for his safety nor to boast about what he had been able to do. Eating honey from the carcass of an "unclean" animal only makes the family ceremonially "unclean"' until evening, if at all, which is no serious violation of dietary laws.

3. Burning the Philistine's fields and food stocks required careful planning, timing, and preparation—hardly an impulsive act.

4. Samson engages in 3 fights with his enemy, the Philistines: he kills 30 and takes their clothing, in a judicial act he slaughters others "hip and thigh," and on his own he is able to kill 1000. He kills an attacking lion in self-defense; when blinded and imprisoned, he is able to pull down a Philistine temple on top of his enemies and himself. All these conflicts are either acts of self-defense or proactive acts of war, not irritability or aggressiveness.

5. Is it not an act of heroism to single-handedly kill 1000 armed and armored enemy troops with no weapon but a dog's dinner, a bone? No recklessness here except the kind of heroism for which he would have received regimental honors in recent wars. Moreover, a close reading suggests Samson and Delilah are in love and he is playing a lover's game as lovers do. He is at ease in her company and unaware that she has a hidden agenda and hidden Philistines awaiting their opportunity. No recklessness or disregard for personal safety here either, just the type of games lovers play when at ease in each other's company.

6. Judges 15:16 is a victory song; Samson has survived against overwhelming odds. Victory is a time for celebration, not remorse.

One of Samson's additional actions listed by researchers for so-called conduct disorder that has not been responded to above is cruelty to small animals. Samson does make incendiaries of 300 foxes (or jackals) and this may be offensive to those who today support animal rights. However, Judges is a book of cruel episodes against men, women, and children and we may not expect harvest pests to be treated better.

Of course Samson's conduct was unacceptable to his fellow Israelites; the tribe of Judah were cowardly betrayers who were at ease with the Philistine enemy and should have known better than to betray a hero who was to be commended in later ancient literature.

History has plenty of examples of characters with ASPD for Altschuler and his fellow researchers to choose for their case studies. Samson deserves better than to be dismissed as an example of *DSM-IV* conduct disorder. Under the circumstances, Samson's behavior is very understandable, even heroic, even acceptable!

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Samson, the Bible, and the *DSM*

In a letter published in the February issue of ARCHIVES, Altschuler et al[1] apply the *DSM* to the biblical hero Samson and suggest that he may have carried the diagnosis of ASPD. Such mechanical use of the *DSM*, in my opinion, both fails to enhance understanding of the person so diagnosed (and may, in fact, unnecessarily stigmatize him) and trivializes the profession.

The *DSM* is an instrument that categorizes various psychiatric and behavioral phenomena within a contemporary cultural context for the purpose of establishing guidelines and improving communication among professionals. It does not endeavor to, nor can it, explore motives or dynamics.

Altschuler et al apply the *DSM* without regard to the mentality and behavioral norms of biblical times. Killing a lion, in a society of warriors and hunters, is mistakenly labeled by them as "cruelty to animals." Similarly, they misunderstand that in such a society, self-praise after vanquishing one's foes is the norm, rather than the antisocial thing to do.

If the authors were to superimpose *DSM* criteria on other ancient characters, every biblical or warlike mythological hero would receive a diagnosis of ASPD, and every ancient prophet would be found to suffer from a delusional disorder or schizophrenia. Such findings, even if accurate, would be merely an exercise in counting symptoms, would shed little light on the psychology of hero or prophet, and would not explain why we resonate with their stories.

In an article entitled: "Samson's Complex: The Compulsion to Re-enact Betrayal and Rage,"[2] I compared the life story of a contemporary psychotherapy patient to that of biblical Samson, suggesting that both the present-day individual and the mythological hero share a distinct behavioral pattern. Both manifest the compulsion to repeatedly reenact the experience of betrayal by a woman, followed by destructive attacks of rage against others and ultimately against their own tormented selves. I named that pattern "Samson's complex" and viewed it as a deep-seated, characterological defect stemming from faulty early attachments. The existential despair and suicidal longings typify men with Samson's complex and strongly suggest that mythical Samson does not fit the profile of a sociopath.

By analyzing a mythical or literary figure in depth, as opposed to enumerating symptoms, it is possible to enrich one's understanding of both the figure and the psychological underpinnings of myth itself.

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In reply

We appreciate the interest in our short letter.[1] *Further discussion here shows (1) with more examples that Samson overwhelmingly meets the criteria for ASPD, (2) the utility of the* DSM *in clear cases, and (3) that the writer of the Samson story, most likely Ahimaaz the Yahwist son of Zadok the Priest, had a remarkable grasp of psychiatric disease as he knew all the criteria for ASPD (see below) and what diseases to exclude.*

Rigorous application of, for example, physical examination and imaging protocols of patients with an acute abdomen, extended scrubbing before surgery, tight glucose control in patients with diabetes, computed tomographic scans to rule out brain tumors, Papanicolaou smears, and vaccination protocols have greatly enhanced the ability to diagnose and treat patients, and do not trivialize their respective specialties. Sadly, there remain many patients with disease beyond the scope of these excellent protocols. Patients are not stigmatized by their diagnosis but by their actions. Burning foxes tied tail to tail or not killing the lion was taken as cruelty to animals.[1] *Specific examples of diagnosis of other historical or mythological figures with ASPD would be of interest. The history of schizophrenia is a vast and fascinating topic. We note that, curiously,*[2] *the only case so far to even possibly pass muster before 1800 is the Poor Tom character in Shakespeare's* King Lear. *Samson killed many people—this is a hard sign. Kutz's patient is not noted to have killed anyone. Samson showed no signs or symptoms of depression, but Dr Kutz's patient is described as being depressed. These issues illustrate the difference between Samson and Kutz's patient, and the essence of ASPD—very violent, dangerous individuals. Understanding the psychodynamic origin of a patient's actions is difficult to do even for a modern patient. Regardless, ASPD has recently been shown, in these* ARCHIVES,[3] *to have a neurologic basis.*

Samson is only at war when he starts one. Similarly, not everyone in Judges is at war. Samson did not burn fields as an act of war but because his father-in-law had given away his wife whom he thought Samson now despised. Failure to follow socials norms is illustrated when your own people try to arrest you. It was deceitful not telling his parents about a serious incident such as killing a lion. Eating honey from a carcass was a violation of dietary laws. Samson also demonstrated deceitfulness or conning in using a riddle that it would be impossible for the interlocutors to answer (Judges 14:12-14). Samson impulsively burned the fields (Judges 15:5). Killing 30 men after losing a bet (Judges 14:19), or burning fields after leaving your wife (Judges 15:5) are aggressive acts, as were Samson's responses to all situations. If one individual takes on one thousand, this one individual would have to believe in having a probability of greater than 99.93% of beating each opponent to even assume to have a 50% chance of surviving the fight. This is reckless disregard of safety of self! So was Samson's telling Delilah the secret to his strength after she tried 3 times previously to kill him. Delilah easily betrays Samson and was not in love with him. If Samson were in love with Delilah, or just trying to bed her, he would have told her the secret the first time, not the fourth. Even after a just war, magnanimity in victory is what true heroes demonstrate. Indeed, necessary healing after the US Civil War began immediately on cessation of hostilities when Union General Joshua Lawrence Chamberlain, hero of the Battle of Gettysburg, who had himself been wounded seriously on multiple occasions ordered his troops to salute their vanquished Confederate colleagues after the surrender was received. As we noted[1] Samson meets 6 of the 7 criteria for ASPD—only 3 of 7 criteria are necessary to make the diagnosis. The only criteria for ASPD that Samson does not meet is failure to meet one's financial obligations. However, the author of the story belies knowledge of this criteria as well when he has Samson repay his bet only by killing 30 men, and using the stolen dead men's garments to pay up (Judges 14:19). Actions such as burning foxes tied tail to tail in a field are cowardly, not heroic or acceptable.

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Rhythmicity in the Regulation of Luteinizing Hormone Release

In the December 2000 issue of the ARCHIVES, Young et al[1] published an excellent article on alterations of the hypothalamic-pituitary-ovarian axis in depressed women, with a follow-up commentary by Halbreich.[2] In their article, Young and colleagues described decreased levels of circulating estradiol in the follicular phase of women with depression. They also report normal frequency and amplitude of the pulsatile release of luteinizing hormone (LH).

This article represents a new and important area of psychoendocrinology. Although there is a growing literature describing the pulsatile release of pituitary hormones in healthy women, this area remains in its infancy in the psychiatric literature. As pointed out by both Young et al[1] and Halbreich,[2] a single peripheral blood assay, or even a stimulation test, cannot find differences in pulsatile release.

We have recently completed a study of LH release in woman with depression.[3] Using methods similar to those used by Young and coauthors, we assayed LH every 10 minutes. Unlike Young and coauthors, we found a slower frequency of LH pulsatility in depressed women; however, this frequency finding is quite sensitive to the algorithm parameters that define a pulse.[4] A more consistent finding described in our pilot study[5] and final article is a disturbance of the rhythmicity of pulsatile LH release found in depressed women. There has been little study of rhythm disturbance in hormones with "ultradian" rhythms such as LH, and rhythmicity may be an important physiologic variable in the regulation of hormone release. It would be interesting to know if a similar rhythm disturbance exists in the data presented by Young et al.[1] This might affect the finding of decreased estrogen.

We certainly agree with the conclusion of Halbreich[2] that future studies should focus on the multidimensional, dynamic interaction of gonadal hormones with the multitude of hormonal and other systems, and we congratulate Young and colleagues for their work.

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Response Differences of Spontaneous Panic and Fear

Gorman et al[1] claim "evidence for a central fear mechanism" in panic disorder (PD). They state the following in their abstract:

Background: *Inhalation of carbon dioxide (CO_2) has been shown to produce more anxiety in patients with panic disorder (PD) than in healthy comparison subjects or patients with most other psychiatric illnesses tested, although premenstrual dysphoric disorder (PMDD) may be an exception. Several reasons have been proposed to explain CO_2 breathing effects in PD. We examined differences in respiratory response to CO_2 breathing in 4 groups to address these issues.*

Methods: *Patients with PD (n=52), healthy controls (n=32), patients with PMDD (n=10), and patients with major depression without panic (n=21) were asked to breathe 5% and 7% CO_2. Continuous measures of respiratory physiological indices were made.*

Results: *Carbon dioxide breathing produced the expected increases in all 4 respiratory variables measured. More patients with PD and PMDD had panic attacks than did controls or patients with major depression. Subjects who experienced panic during 5% or 7% CO_2 inhalation had the most extreme increases regardless of diagnostic group. Among patients with PD, baseline end-tidal carbon dioxide levels were significantly lower in those who subsequently had a panic attack during 5% CO_2 breathing than those who did not.*

Conclusions: *Although CO_2 breathing causes a higher rate of panic attacks in patients with PD than other groups (except PMDD), the physiological features of a panic attack appear similar across groups. Once a panic attack is triggered, minute ventilation and respiratory rate increase regardless of whether the subject carries a PD diagnosis. These findings are compatible with preclinical fear conditioning models of anxiogenesis.*[1(p125)]

However, Gorman et al[1] attempt to judge the comparative value of 2 views:

(1)"The susceptibility of patients with PD to high levels of anxiety during CO_2 breathing represents a specific abnormality in the afferent neural pathways"[1(p125)] (referring to Klein[2]).
(2)"Carbon dioxide breathing produces a sense of air hunger- . . . highly reminiscent of . . . naturally occurring panic. The nonspecific somatic distress produced by CO_2 inhalation- . . . triggers the panic attack."[1(p125)]

My main point is that spontaneous panic is not simply equivalent to fear as shown by symptomatic, physiological, and treatment response differences.

Discerning the relative merits of differing formulations requires a meticulous look at the comparative theoretical fit of the entire range of incompatible and compatible observations. As described herein, no evidence is presented *for* a central fear mechanism. Certain peripheral physiological resemblances are claimed, but disconfirming evidence is ignored.

The criteria for PD distinguish anticipatory anxiety from the attack itself. Anticipatory anxiety is often associated with increments of cortisol. However, a distinctive feature of spontaneous, as well as CO_2- and lactate-induced panic attacks, is the counterintuitive lack of hypothalamic-pituitary-adrenal activation. Furthermore, the acute dyspneic air hunger of these panic attacks are not features of danger-incited fear. Unfortunately, Gorman et al[1] do not discuss such incompatible observations.

This précis of the suffocation false alarm theory of the panic attack does not attend to its broader features. To quote,

> A carbon dioxide hypersensitivity theory of panic has been posited. We hypothesize more broadly that a physiologic misinterpretation by a suffocation monitor misfires an evolved suffocation alarm system. This produces sudden respiratory distress followed swiftly by a brief hyperventilation, panic, and the urge to flee. Carbon dioxide hypersensitivity is seen as due to the deranged suffocation alarm monitor. If other indicators of potential suffocation provoke panic this theoretical extension is supported. We broadly pursue this theory by examining Ondine's curse as the physiologic and pharmacologic converse of panic disorder, splitting panic in terms of symptomatology and challenge studies, reevaluating the role of hyperventilation, and reinterpreting the contagiousness of sighing and yawning, as well as mass hysteria. Further, the phenomena of panic during relaxation and sleep, late luteal phase dysphoric disorder, pregnancy, childbirth, pulmonary disease, separation anxiety, and treatment are used to test and illuminate the suffocation false alarm theory.[2(p306)]

Therefore, this theory goes well beyond a theory of a sole abnormality in peripheral, afferent, CO_2-responsive pathways to hypothesize that a hyperreactivity of a common human adaptive mechanism—the suffocation alarm system—provides a more specific explanation of spontaneous panic attacks than considering the panic attack as simply conditioned fear. Whether peripheral abnormalities exist as in the carotid body is an empirical matter, not a theoretical necessity.

As elaborated in my text[2] and elsewhere,[3] panic is dealt with in a variety of contexts, such as late luteal phase disorder (PMDD) and "mass hysteria." A strength of the theory is that it offers explanations of several facts (eg, that enclosed spaces with no air motion often foster panic) that are not deducible from an associative fear theory.

That imipramine, after some weeks, blocks the spontaneous panic attack was a seminal finding. However, imipramine and other antipanic agents such as selective serotonin reuptake inhibitors have no effect on ordinary fear. The adverse effects of imipramine include tachycardia, dry mouth, sweating, and tremor, which should incite panic if conditioned fear is causal.

In addition, the hypothesis of a discrete suffocation alarm is supported by the joint lack of CO_2-induced feelings of suffocation and ventilatory responses in Ondine's curse (congenital central hypoventilation syndrome), indicating that air hunger is a specific evolved adaptation to potential suffocation. Since air hunger is not part of ordinary fear but is central to spontaneous panic, panic differs from fear.

The argument by Gorman et al[1] that CO_2 inhalation causes nonspecific distress, which by reminiscence incites a fearful reaction, parallels the claim that the induction of panic attacks by intravenous lactate in patients with PD was caused by a fearful reaction to nonspecific stress. Since numerous other distressing infusions do not produce such panics (eg, 5-hydroxytryptophan, physostigmine, insulin, EDTA, etc), this argument is not

cogent. More directly relevant to the CO_2 context is the fact that simple hyperventilation, which should be reminiscent of panic-associated hyperventilation, is an infrequent panicogen as Gorman et al[4] demonstrated.

It is also not revealed that the patients with PD who panic when breathing CO_2 are a subset of those who panic because of lactate, indicating a commonality for these agents, whereas those few who panic and hyperventilate while breathing room air have no systematic relation to the other challenges.

Turning to study details, the measurements by Gorman et al[1] are restricted to the first 5 minutes of CO_2 inhalation to preserve "meaningful" sample size, although the average time spent inhaling 5% CO_2 for each group ranged from 16 to 20 minutes. Other studies have analyzed complete challenge records.[5-8] Since the most acute respiratory changes occur approximately 1 minute prior to panic,[9] the measures obtained are only distantly related to the panic crescendo. Therefore, the lack of ventilatory differences found between diagnostic groups has, at best, modest probative value to support the claim that the ventilatory pattern of panic is not relevant to diagnosis.

Gorman et al[1] question, "Is increased ventilatory response to CO_2 breathing specific to patients with PD, or does it occur in any person having a panic attack?"[1(p126)] They go on to say, "To maximize the size of cells and still address the primary question, we performed an analysis of PD vs all other groups combined."[1(p127)]

However, it is already known that PD and PMDD have similar panic/ventilatory reactions to CO_2 (and lactate). This confounded contrast obscures respiration-related diagnostic differences (which might be a feature of depression and nonillness) as well as any interactions with eventual panic status. Therefore, inferences affirming the diagnostic nonspecificity of CO_2-induced respiratory reactions are not justified by these null findings.

This caveat also holds true for the conclusory statement, "Increased respiration also predicted panic in 2 other groups in this study. Hence, baseline respiratory activity also seems to be a diagnostically nonspecific aspect of CO_2 panic."[1(p130)] Unfortunately, the data and analysis are not shown.

A less critical issue is that no proper, direct, statistical analyses are presented to support their conclusion: "For all measures, the response to 5% CO_2 varied more in respect to whether a panic attack occurred than whether the subject had PD."[1(p129)] More important, even if the respiratory patterns anteceding CO_2-induced panic were identical for all diagnoses, the only invalidated theory would be one affirming that such respiratory reactions are uniquely restricted to PD. However, as already indicated, the theoretical presentations[2,3] dealt extensively with panic attacks in a range of diagnostic and environmental circumstances. Therefore, the claim for conditioned fear theory superiority, based on supposed evidence of diagnostic nonspecificity, does not follow.

This conditioned fear theory is presented as a novel advance by Gorman et al[1] as well as by Roy-Byrne and Stein[10] in their commentary. However, the belief that panic is a realistically unwarranted fear release was common to both psychoanalytic and behavioral theories. The suffocation false alarm theory was stimulated by observations that did not fit these conventional views.[11]

I emphasize that acute air hunger and dyspnea, salient features of spontaneous panic, are not characteristic of fear. Furthermore, a salient symptomatic feature of fear does not occur in panic. Acute terror, as on the battlefield, often leads to loss of bowel and bladder control, probably due to overriding parasympathetic activation. This has not been reported as a PD characteristic despite common acute fears of imminent death. This is consistent with the acute vagal withdrawal postulated to incite abrupt tachycardia in panic attacks.[12]

Prior human brain imaging studies of CO_2 effects, although relevant to the speculations of Gorman et al[1] regarding fear-related neurocircuitry, are not cited.[13,14] Of interest is that these studies found cerebellar activations, which are not deducible from a simple conditioned fear model. Recently, controlled positron emission tomography studies by Parsons et al[15(p2041)]

> assessed cerebellar responses when the urge to breathe is stimulated by inhaled CO_2 . . .. The conjoint physiological effects of hypercapnia and the consequent air hunger produced strong bilateral, near-midline activations of the cerebellum . . .. The primal emotion of air hunger, dissociated from hypercapnia, activated midline regions of the central lobule. The distributed activity across the cerebellum is similar to that for thirst, hunger, and their satiation . . . the cerebellum has a comparable role in other vegetative functions accompanied by compelling primal emotions. One such function is air hunger.

Extended analyses by Brannan et al[16] and Liotti et al[17] also emphasize specific brain circuits underlying air hunger. Brannan et al[16(p2029)] state the following:

> Regulatory physiologic processes occur continuously beyond the realm of consciousness, and only rarely . . . do they intrude and dominate conscious awareness . . . "hunger for air" is one process capable of making such an imperious intrusion. Intense breathlessness occurs in certain psychiatric states such as panic disorder (theorized to be due to a malfunction of the "suffocation alarm").

Brannan et al[16(p2034)] conclude that

> the striking response of limbic and paralimbic regions to CO_2 stimulation points to these structures having a singular role in the affective sequelae entrained by disturbance of basic respiratory control whereby a process of which we are normally unaware becomes the salient element of consciousness. We propose that rostral and ventral ACC [anterior cingulate cortex], hippocampus and parahippocampus, amygdala, insula and fusiform gyrus, along with deactivations in dorsal anterior and posterior cingulate and prefrontal cortex represent a distributed network involved in the affective representation and/or regulation of breathing. Their dysregulation may play a role in the breathing abnormalities observed in panic disorder as well as other emotional disorders.

Modern studies have shown a remarkable modularity of brain function. Seemingly singular perceptions or responses incorporate multiple discrete component functions. Vital requirements such as air, food, and water require distinctive perceptual/emotional/motivational brain circuits that should not be subsumed under a fear circuit that, by conditioning, serves all purposes.

I agree with Gorman et al[1] that neuroimaging affords a new, more direct, approach to brain circuitry, but it is precisely by relating the experimental manipulation of such circuits to specific evolved organismal adaptations that circuit functions become understandable.[18]

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The Structure of the *DSM*

In his article on the structure of common mental disorders, Krueger[1] reports on the analysis of comorbidity data obtained in a sample of 8098 noninstitutionalized US civilians in the National Comorbidity Survey. The analysis is carried out using confirmatory factor analysis. The confirmatory factor analysis yields a 3-factor model that accounts reasonably well for the obtained covariance between several mental disorders. This leads Krueger to conclude that "The results offer a novel perspective on comorbidity, suggesting that comorbidity results from common, underlying core psychopathological processes."[1(p921)]

However, diagnoses were made using the criteria of the *DSM-III-R* "without the imposition of hierarchical exclusionary rules."[1(p922)] Although this is fine as long as correlations among disorders are interpreted as reflecting comorbidity patterns, a problem arises when the obtained correlations are subjected to a confirmatory factor analysis and the resulting factors are interpreted as "underlying core psychopathological processes." This problem is touched on by Wittchen et al[2] in their commentary on Krueger's article. Some disorders (eg, dysthymia and depression) have a number of criteria in common, whereas other disorders (eg, dysthymia and social phobia) do not. If diagnoses are made without hierarchical exclusion rules, disorders having more criteria in common will tend to covary more than disorders having fewer criteria in common. However, finding this does not provide "new" empirical information; it is a direct result of the way the *DSM* is structured. In other words, given the *DSM*, these are the results you will find.

In fact, almost the entire correlation matrix reported by Krueger follows the pattern one would expect from the structure of the *DSM*. The **Table** contains the original correlation matrix and the number of common criteria for each pair of disorders. The correlation matrix and the common criteria matrix have a similar structure: the greater the number of common criteria, the higher the correlation between the disorders.

The similarity between the correlation matrix and the common criteria matrix is further demonstrated by a Spearman correlation of 0.62 between the number of common criteria and the associated value of the correlation. This suggests that, if the correlation matrix were conditioned on the number of common criteria, one would be left with a variance-covariance matrix without structure (except for the part involving alcohol dependence, drug dependence, and antisocial personality disorder, where the correlations are higher than one would expect from the number of common criteria alone).

The question of whether mental disorders are better conceptualized in terms of latent dimensions or in terms of types represents a matter of great interest in psychopathology. However, the results presented in Krueger's article do not supply information that is empirically relevant to this issue. For an observation to be empirically relevant to a hypothesis or theory, the observation must be predicted jointly from the premises of the theory and secondary premises—involving, for instance, the measurement apparatus used—but not from these secondary premises alone.[3] Krueger's results can be predicted solely from secondary premises (namely, from the fact that the *DSM* was used for diagnosis) without any reference to latent dimensions or core psychopathological processes.

Shared *DSM* Criteria for the Mental Disorders Reported by Krueger[1]*

Disorder	Disorder									
	MDE	DYS	AGPH†	SOP	SIP	GAD	PD	AD	DD	APD
MDE	All (1.00)									
DYS	6 (0.69)	All (1.00)								
AGPH†	0 (0.44)	0 (0.29)	All (1.00)							
SOP	0 (0.40)	0 (0.32)	2 (0.54)	All (1.00)						
SIP	0 (0.46)	0 (0.33)	2 (0.58)	6 (0.59)	All (1.00)					
GAD	4 (0.59)	3 (0.64)	1 (0.44)	1 (0.36)	1 (0.42)	All (1.00)				
PD	0 (0.50)	0 (0.40)	3 (0.59)	1 (0.40)	0 (0.52)	7 (0.59)	All (1.00)			
AD	0 (0.31)	0 (0.31)	0 (0.15)	0 (0.24)	0 (0.22)	0 (0.27)	0 (0.18)	All (1.00)		
DD	0 (0.30)	0 (0.29)	0 (0.27)	0 (0.26)	0 (0.25)	0 (0.34)	0 (0.32)	0 (0.66)	All (1.00)	
APD	0 (0.19)	0 (0.27)	0 (0.20)	0 (0.28)	0 (0.12)	0 (0.26)	0 (0.11)	0 (0.60)	0 (0.62)	All (1.00)

*Data given as the number of shared criteria, with the corresponding tetrachoric correlation in parentheses. MDE indicates major depressive episode; DYS, dysthymia; AGPH, agoraphobia; SOP, social phobia; SIP, simple phobia; GAD, generalized anxiety disorder; PD, panic disorder; AD, alcohol dependence; DD, drug dependence; and APD, antisocial personality disorder.

†The *DSM-III-R* description for AGPH does not list separate criteria but a compound description of criteria; I counted the criteria mentioned in the description separately.

Consequently, his results cannot be regarded as evidence for such processes.

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In reply

It has been very gratifying to see so much interest in my recent work on comorbidity among common mental disorders,[1] as evidenced by the letter from Borsboom and the recent replication and extension by Vollebergh et al.[2] I will offer a few brief remarks on some of the points raised in Borsboom's letter.

Borsboom suggests that the factor structure of common DSM *mental disorders[1,2] could be attributed to overlapping criteria among the disorders. The majority (33 of 45) of the correlations among the mental disorders I studied were unaffected by shared criteria (see Borsboom's table). In fact, all the correlations bearing on the question of whether the National Comorbidity Survey data support a coherent externalizing factor that is distinct from the internalizing factor were unaffected by shared criteria. The issue of overlapping criteria is relevant only to the mood and anxiety disorders (ie, only correlations among these disorders have criterion overlap values greater than 0 in Borsboom's table). Can correlations among these disorders be understood by proposing a broad and coherent factor linking them, as opposed to attributing the relationships solely to criterion overlap? Consider the following 5 points.*

First, the mean tetrachoric correlation among lifetime internalizing disorders in the National Comorbidity Survey that share no criteria was 0.41 vs 0.54 for those that share 1 or more criteria. That is, comorbidity among internalizing disorders cannot be attributed solely to shared criteria. Internalizing disorders that share no criteria show moderate correlations that are similar to the moderate correlations among internalizing disorders that do share criteria.

Second, the criteria shared among some lifetime disorders may have been present at different times in a person's life. For example, the sleep problems that contributed to a diagnosis of generalized anxiety disorder during one period need not be the same sleep problems that contributed to a diagnosis of major depression during a different period. Hence, symptom overlap cannot completely explain lifetime comorbidity patterns. Moreover, both lifetime and past-year time frames have yielded similar overall comorbidity patterns in our work to date, suggesting that the diagnostic time frame does not have a major impact on the factor structure of common DSM *mental disorders.[1,2] The authors of the original commentary on my article[3] also overlooked this finding and its relevance to understanding comorbidity patterns. Specifically, the authors of the commentary overlooked the paragraph[1(p924)] in which I reported that findings using 12-month disorders were similar to findings using lifetime disorders, as well as an earlier article of ours employing only past-year disorders.[4] These considerations should reassure us that the structure of common mental disorders is not an artifact of a particular time frame, and, moreover, that lifetime patterns of comorbidity cannot be attributed solely to criterion overlap.*

Third, hierarchical exclusionary rules are sometimes proposed as a way of allowing for both shared criteria and distinct, categorical disorders, but this approach is often unwieldy and problematic. For example, complex exclusionary rules were employed in DSM-III *but were largely abandoned because they were rather cumbersome. Fortunately, there is a better way to accommodate both specific and nonspecific symptoms via psychometric models. Extensive psychometric work supports a model of internalizing disorders in which each disorder contains both a specific, unique component of variance and a general, shared component of variance.[5-7]*

Fourth, covariance among mood and anxiety disorders likely represents a shared neurobiological substrate, as recognized by many psychopharmacologists.[8] Understanding the neurobiological characteristics of such shared substrates will substantially advance our understanding of their pathological manifestations. This is not to say that there is

no utility in characterizing the distinctive ways in which these substrates can be manifested in particular persons. It is simply that these variants may be better characterized as facets (or subfactors) of a broader factor, rather than as distinct categories of disease.

Finally, criterion overlap among mood and anxiety disorders, although not capable of explaining the full extent of the comorbidity among these disorders, supports rather than challenges a common substrate model. Such overlap underlines the indistinctiveness of these disorders; this indistinctiveness could be attributable to a shared, underlying substrate.

One of the major goals of my work has been to illustrate how the comorbidity phenomenon is difficult to reconcile with a strictly categorical model of mental disorder but can be understood from a dimensional perspective. I remain hopeful that my work will help other researchers and clinicians to pursue the further development of dimensional models of psychopathological characteristics. Simply put, many patients represent blends of putatively distinct psychopathological characteristics, and describing these persons as suffering from multiple mental disorders is often awkward and, in many cases, might also be misleading. Fortunately, psychopathological blends can be accommodated within dimensional models because these models allow persons to be described along multiple dimensions simultaneously. We must continue to develop these models and work to incorporate them more fully into both research and clinical practice.

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Atypical Antipsychotics and Cognition in Schizophrenia

Purdon et al[1] have presented, with many qualifications, results from a double-blind randomized trial comparing the cognitive benefits of olanzapine, risperidone, and haloperidol. Studies of this type are important; however, the interpretation of the referenced study requires caution, and the clinical relevance of the data is limited.

In disclosing the increasing interest in slower titration and lower doses of risperidone than were used in the trial, the authors assert that the dosing schema they used was valid because it was consistent with the relevant product monograph and with the doses used in an earlier study.[2] Emerging data and clinical practice often lead advances in the standard of care, and changes to product literature lag behind. Also, the study that was cited for setting a dosing precedent was conducted in a refractory population that can be expected to require higher medication doses. A more credible discussion of the aberrantly high doses of risperidone used in the trial would be made by using audited pharmacy data to get a realistic assessment of the average daily doses used in practice at the participating centers.

Also unaccounted for is the fact that the increasingly large doses of risperidone administered affirmatively influenced the need for anticholinergic medication. It has been well established that anticholinergic medication has an effect on new learning and memory.[3] In this study, the only significant finding after multiple analyses was that olanzapine was more beneficial to immediate recall. Immediate recall is impaired by anticholinergic medication; thus, the changes noted can be explained almost entirely by the anticholinergic usage demanded by the unrealistically high risperidone dose, which leaves the Hooper Visual Organization Test as the only finding available for Bonferroni adjustment.

The diminution of statistical power caused by attrition is noted. This is always a concern, and in this study, the dropout rate exceeded 50%; however, if the study is powered under the assumption that there will be a certain number of dropouts, then this is no longer a concern. Unfortunately, nowhere in the article do the authors mention power or sample size justification for their analyses.

In the face of these qualifications and flaws, the conclusion that olanzapine is a superior drug is not well supported by the evidence presented. Of 17 tests used, olanzapine was superior to risperidone in only 2 after correction for repeated testing, and the effects observed in the immediate recall domain are most likely the result of anticholinergic use. Both agents are shown to enhance cognition in schizophrenia; however, additional work needs to be done to determine, with accuracy, the relative cognitive benefits of these agents.

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Improvement of Cognitive Dysfunction After Treatment With Second-Generation Antipsychotics

Dr Purdon and colleagues should be commended on their efforts to study the highly important issue of long-term cognitive changes when patients with schizophrenia are treated with different antipsychotic drugs.[1] Their report raises many issues that we discuss in this letter.

In addition to assessing psychopathology, all patients were studied using a neuropsychological test battery measuring cognitive functions in 6 domains (motor skills, attention, verbal fluency and reasoning, nonverbal fluency and construction, executive skills, and immediate recall). From these 6 domains, the authors computed a general cognitive index. They conclude that olanzapine has statistically significant advantages over both risperidone and haloperidol in the general cognitive index. All statistically significant differences between groups with regard to the 6 domains of cognitive functions fell victim to an α correction for multiple testing. In a within-group analysis, olanzapine showed significant advantages in only 1 of 6 specific cognitive domains (immediate recall) and in 1 of 17 individual tests.

One cannot fail to notice that both the methods and the presentation of this report are not without problems. It seems that the number of patients allocated to this study (21 and 23 per group) was rather small given recent suggestions that about 64 patients per group would constitute a meaningful sample for such a study.[2] This may be one of the reasons why the authors failed to demonstrate statistically significant differences with respect to the 6 cognitive domains after Bonferroni adjustment. We note in passing that more effective statistical procedures are at hand when faced with the problem of a large number of dependent variables. These include Holm's modification of the Bonferroni correction procedure,[3] or the use of multivariate data techniques such as factor analysis, by which the multiple testing problem could have been largely reduced.

One might also be interested in whether the high number of dropouts (>50%) challenges the conclusions drawn from this study. It could be assumed for instance, that patients who dropped out did so because they either did not improve or did not tolerate one of the study drugs. Moreover, patients may have dropped out for different reasons in the different treatment arms, thereby adding additional variance to an already not very homogenous sample.

These factors add to the problem that we may assume that the sample studied was a highly selected one to begin with, as only a restricted number of patients suffering from schizophrenia will be able to complete an ambitious neuropsychological test battery, which in our estimation takes at least 2.5 hours to complete.

In this context, the last observation carried forward (LOCF) method seems to be quite problematic when applied in a long-term study. Results may be severely biased when the last observation before a patient's withdrawal is just before a subsequent deterioration. Alternatively, the authors might have considered using methods adopted from the analysis of survival data to deal with the problem of "censoring."

The present study, in addition to many others, neglects the fact that many of the neuropsychological tests used are (1) polyfactorial and (2) not independent of each other. Trail Making Test B, for instance, has a motor, attentional, and executive component. It can be expected that patients that have impaired motor skills will not do well on tests that depend on motor skills because patients need to draw or write to complete them.[4] Most neuropsychological functions will be influenced by even mild extrapyramidal motor side effects as demonstrated in patients with Parkinson disease.[5] Although at the end of the day only a specific drug's net effect on cognitive functions is of clinical relevance, we would still like to see whether this is a true drug effect or only an indirect effect, caused by the lower rate of extrapyramidal symptoms in one of the treatment arms. In regard to this, before Bonferroni correction, olanzapine showed advantages over risperidone only in cognitive domains with a large motor skill component.

We were also surprised to read that the authors had used normal control data from the 1970s to validate their general cognitive index. In addition, the construct validity of this index seems to be compromised by the fact that it indicated statistically significant improvement despite the fact that none of the domains it is composed of improved significantly.

Clearly, other side effects and/or features of psychopathology, such as sedation or depression, are also likely to influence cognitive functions. We realize that it may be difficult to account for such intervening variables, especially in a long-term study, but at least we would like to see these issues mentioned in a discussion section. Some mention of the motivation of patients who participate in such studies and the measures undertaken to boost motivation could also be of interest to the reader.

In studies of long-term drug treatment effects, there are additional problems of repeated-measures designs in that practice effects must be considered. The authors tried to control for this by using paired alternate forms for all tests of immediate recall, but according to the study protocol, the same test form was administered to the patients after 6 months. As there was no control sample, a learning effect cannot be ruled out. To complicate matters, this learning effect may have been affected by comedication.

The brief washout from previous drug treatment (2-9 days) adds to the difficulties of interpreting this report. Different types of pretreatment may have had different consequences on cognition. Therefore, baseline-endpoint differences may also be influenced by pretreatment in so far as a patient, whose cognitive functions at

baseline are still impaired by pretreatment, may have a higher likelihood of cognitive improvement.

Lastly, there is incomplete reporting of adjunctive medication that patients could receive "as required." Although the authors indicate that quite a few patients were treated with anticholinergic drugs and that this may have influenced their findings, they do not specify other concomitant medications like benzodiazepines, antidepressants, or other somatic treatments that may have had independent effects on cognition.

In summary, these comments are meant to underscore the conclusion of Purdon et al that their study needs replication.

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In reply

Dr Sharma's criticism of the neuropsychological comparison of olanzapine, risperidone, and haloperidol[1] accurately suggests that the dose of the treatments may be relevant to the results. A recent demonstration of the value of relatively low-dose risperidone in the alleviation of psychotic symptoms in patients with early phase schizophrenia who were treated for more than 1 year[2] provides the first direct empirical support for the comments of Dr Sharma regarding the potential value of similarly low doses of risperidone in treating the cognitive deficits associated with schizophrenia. As Dr Sharma acknowledged, my colleagues and I advised caution in generalization beyond the particular sample and dose ranges examined in our study, and we speculated on the importance of further studies with risperidone, given a perceived trend toward the use of lower doses in clinical practice. Although a stratification analysis failed to detect cognitive improvement from risperidone in the low-dose conditions, and we did not detect additional cognitive improvement in the risperidone subsample not receiving anticholinergic supplements, it is possible that larger-sample investigations with greater power to detect smaller effect sizes and a broader dose range for risperidone may produce results different from the reported findings. However, Dr Sharma's characterization of our dose range as "aberrant" or "unrealistic" seems to be overzealous. Prior to the recently published low-dose study,[2] the assumption of value from low-dose risperidone was based on anecdotal reports from clinicians, whereas an optimal dose range of 4 mg to 10 mg per day was advised in the product monograph and supported by a large-sample study that had used a flexible dose strategy[3] and by a naturalistic survey of 2657 patients in Spain.[4] Moreover, the actual dose of risperidone used in our study[1] was flexible within the range of 4 mg to 10 mg per day, and the clinician responsible for the care of each patient determined the dose deemed necessary for symptom management. The discrepancy between the daily dose required in the low-dose study[2] and that of our study could relate to a variety of patient-specific or clinician-specific features. For example, the low-dose report indicated that 25% of the patients assigned to risperidone had their regimens discontinued and were assigned to treatment with clozapine or a depot first-generation neuroleptic, perhaps relating to difficulties in sustaining the low-dose strategy in a subsample of patients. Additional data are required to confirm the general value of the low-dose strategy to patients with schizophrenia and to evaluate the possibility of a greater cognitive change with a lower dose of risperidone.

The opinions submitted by Dr Weiss' group are less focused, and they consist of a lengthy list of design features speculated to be relevant to the outcome of this study but that are not articulated with sufficient clarity to impeach the observed results. For example, they expressed dissatisfaction with the lack of control of prestudy medications, the absence of a list of adjunctive medications, the age of some of the cognitive tests, and the internal consistency of the cognitive domains. Contrary to the suggestion that prestudy medications be neglected, the study included a fairly sophisticated downtritration schedule leading to the medication-free baseline assessment. Also, all patients were randomly assigned to 1 of the 3 study medications, and the resulting groups were relatively homogenous. Contrary to the suggestion that adjunctive medications were not addressed, the manuscript included a supplementary analysis and detailed discussion of potential anticholinergic effects. This was deemed necessary because there was a differential use of anticholinergic medications in the 3 treatment arms, and there is sufficient published evidence to anticipate an anticholinergic effect on cognitive skills. Other supplements were used relatively infrequently, and there was no strong suggestion of a differential representation in the treatment groups. Dr Weiss' group is correct in their assertion that attrition is a potential problem, particularly if it results in an alteration of the composition of the treatment groups along a dimension that is relevant to the outcome measure. However, this is a potential problem with all longitudinal investigations—not at all unique to the present examination, and the average number of days using the treatment were relatively equivalent across the 3 treatment arms. The only observed difference between the 3 groups concerned the haloperidol arm, which lost a substantial number of subjects prior to the second cognitive assessment. The characteristics of this early termination sample were presented in detail in our original article.[2] Dr Weiss' group also queries the use of instruments with normative data from the 1970s, an odd critique given that some of our most relevant clinical

tools have an even longer history (eg, Abnormal Involuntary Movements Scale, Brief Psychiatric Rating Scale), which attests to their clinical value and utility, not to their obsolescence. The selection criteria for the particular cognitive instruments are discussed in the original article[1] and in greater detail in the companion methodological reviews.[5,6] In brief, the measures were selected for their relevance to schizophrenia, good psychometric properties, and clinical value. Aside from avoiding novel experimental tools, the age of the tests was not considered and continues to be irrelevant to inclusion or exclusion decisions. Dr Weiss' group also suggest that the cognitive domains may lack construct validity because change was observed in a domain despite the lack of change on particular tests within that domain. Applied to ratings of clinical symptoms, such as the Positive and Negative Syndrome Scale (PANSS), this suggestion would lead to the erroneous inference that the PANSS positive score lacks internal consistency unless both the syndrome and the individual symptom scales show a significant change with treatment. Multiple tests were used to increase the sensitivity of the instrument to a variety of skills within a given domain, and to a variety of skill levels within a particular sample. The result is a tool that is invariably more sensitive to treatment effects than individual measures and that will detect change in relatively small sample sizes. The rationale for this approach is described elsewhere,[5,6] and the utility of the approach has been demonstrated in several investigations.[7-9]

Dr Weiss' group offers speculation on a variety of features that may have diminished the power of the study to detect significant differences. Sample size is mentioned, for example, but there is no acknowledgement that this study has reported the largest cognitive investigation of patients taking olanzapine to date and the only direct comparison of the cognitive effects of novel medications. They also suggest that the Bonferroni correction of α in the exploratory analysis may have been too conservative, and they offer alternatives in the form of a more liberal correction method or a factor analysis prior to parametric comparisons. The emphasis on statistical power seems to underscore a preoccupation with the exploratory analysis of the particular cognitive domains or tests that might be most sensitive to change, which in turn tends to overlook the primary purpose of the study, which was to detect changes on the general cognitive index as a result of treatment. The study design was sufficiently powered to detect the robust improvement from olanzapine and the circumscribed improvement from risperidone; the lack of change with haloperidol replicates prior results and is unlikely to reflect a lack of statistical power. Other studies have also detected significant changes with smaller sample sizes,[7-10] and this work has not yet been added to the meta-analysis cited as expert opinion to justify larger sample sizes.[11] The Bonferroni correction of the α level in our exploratory analyses was intentionally selected for its highly conservative values in an effort to not overstate the relevance of particular domains or tests of cognitive skills. Also, the purpose of the exploratory analysis was not to isolate the most basic cognitive process that might underlie the cognitive change to treatment, but to provide a domain- and test-specific comparison through time that might assist future investigators in their selection of appropriate instruments from among the cognitive tools commonly used in clinical practice. An application of factor analysis may have allowed a more liberal α correction, but it would have diminished or eliminated the application of the results to general clinical practice. Consider, for example, a report showing differential medication effects on novel combinations of symptoms derived from a factor analysis of a large group of positive, negative, depressive, and extrapyramidal symptoms. Although testing the change on novel factors 1, 2, 3, and so on, might be of scientific interest, the clinical relevance of the demonstration would be dubious.

Dr Weiss' group has also suggested that results of the present study may lack general relevance to schizophrenia because of various selection biases that may have produced an unrepresentative sample. Potential problems with use of the last observation carried forward as an endpoint measure are noted at length by this group, but again, they do not acknowledge that this is an issue that is relevant to all longitudinal studies of schizophrenia. A variety of scenarios can be constructed, but Dr Weiss' group note in particular a potential performance decline that may occur at the last observation and thus influence the endpoint analysis. For example, if the last observation is obtained when the subject is withdrawing from the study during an acute exacerbation of symptoms or adverse effects, then the clinical, safety, and cognitive measures will be obtained at the low point in the course of treatment, and hence, not be truly representative of the treatment effects. This touches on a much larger debate concerning whether we should report the best or the worst overall effects of treatment, but this is not an issue that will be resolved here. However, unlike most of the prospective treatment studies published to date, the potential difficulty with using the last observation for the endpoint analysis was acknowledged in our article, and efforts were made to limit the relevance of this potential problem. Unmentioned or overlooked by Dr Weiss' group was the use of a mixed analysis of variance for examination of the last observation carried forward (preferable to their suggested survival analysis), as well as an analysis of complete cases (presented in a table footnote) that is less likely to be influenced by the potential problems with the last observation carried forward. The 2 analyses gave similar results, except for risperidone, which did not produce a significant improvement in the analysis of complete cases. This seems to contradict Dr Weiss' group's suggestion of more cognitive impairment at the time of discontinuation, as the results from the haloperidol and olanzapine groups remained constant across the 2 analyses, and contrary to their expectations, the risperidone group showed cognitive benefits in the analysis with the last observation carried forward that were not apparent in the analysis with complete cases.

The suggestion that the cognitive assessment battery might itself produce a selection bias by excluding patients unable to complete the testing is entirely without foundation. Almost without exception, patients with schizophrenia are able to complete extensive test batteries; this is true within my regular clinical practice, where we examine more than 100 patients with schizophrenia each year, as well as

in formal studies of patients with early phase schizophrenia,[1] patients with chronic schizophrenia,[9] and those with partially treatment-refractory illness.[7,8] Within the present study, only 3 of the 65 patients followed up in this study (ie, less than 5%) were unable to complete the entire battery of tests at baseline; although these patients did not continue with the protocol, not one of them, nor any of the patients that withdrew during the course of 1 year's treatment, cited dissatisfaction with the testing protocol as their reason for withdrawal. As one might anticipate, the most common reason for discontinuation from this study was related to adverse treatment effects (entirely consistent with other longitudinal treatment studies), and not to the extra attention the patients received during the cognitive evaluation. In all of our studies, highly skilled and compassionate psychology assistants can obtain a complete battery of tests on almost any patient with schizophrenia. Contrary to the speculation offered by Dr Weiss' group, that patients able to complete prolonged testing batteries are not representative of the more general sample of patients with schizophrenia, in both my clinical work and in previous studies I have consistently observed the opposite. Patients with schizophrenia who are unable to complete a neuropsychological test battery are not representative of the general sample. I agree with the contention that the results may apply to patients capable of completing an extensive test battery, and I would add that this fortunately seems to include almost all patients with schizophrenia.

Space limitations preclude a thorough discussion of all issues raised by Dr Sharma and by Dr Weiss' group, but their letters indicate a commitment to improved experimental design in this area, and I am grateful for their thought and attention in this regard. Further work in this area is essential to establishing the reliability of the results and the critical parameters behind cognitive changes related to treatment.

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