succinylcholine chloride (2 mg/kg) and the monkeys were ventilated with positive pressure 100% oxygen. Seizure expression was monitored via scalp electroencephalography (EEG), electromyography, and visuomotor manifestations in a nonparalyzed limb. One subject (No. 1) had a chronically implanted intracerebral multicontact electrode in place, permitting recording of intracerebral EEG and TMS-induced voltage.[5]

The 2 trials with the commercial device did not produce a seizure. In contrast, each of the subsequent 8 trials with the custom device produced a generalized tonic-clonic seizure ranging in duration from 10 to 20 seconds, documented by motor manifestations, electromyography, scalp EEG, and intracerebral EEG results. Intracerebral recordings documented that peak induced voltage with the custom TMS device matched that achieved with electroconvulsive shock and occurred in the prefrontal cortex. The commercially available device achieved less than half the voltage induced by electroconvulsive shock.[6]

Magnetic seizure threshold was titrated by administering trains of increasing duration until a generalized seizure was induced. Due to coil heating, no more than 2 trains could be administered in a single session. Thus, the various train durations were administered across 4 sessions. Seizures were reliably obtained with parameter settings of 40 Hz, 90% of maximal stimulator output, administered for 4 to 5 seconds. This represents stimulation at more than 400% of the electromyographically defined motor threshold. Stimulation at this intensity is far in excess of recommended safety guidelines for human use of subconvulsive rTMS.[7] The purpose of this experiment, however, was intentional seizure induction, and high intensities were needed to overcome the anticonvulsant effects of anesthesia.

These findings demonstrate the feasibility of rTMS seizure induction under general anesthesia. The fact that the commercial device was incapable of eliciting seizures suggests that the broader pulse width and/or faster frequency of the custom device were needed. Future work will focus on parameterization and safety to support clinical use in humans as a novel convulsive treatment. The enhanced control over dosage and focality achieved with rTMS may offer the capacity to focus seizure induction in the prefrontal cortex, thereby improving the efficacy and limiting the cognitive side effects due to medial temporal lobe stimulation. This animal model in which magnetic seizure threshold can be easily assessed, will provide information relevant to safety guidelines for the human use of nonconvulsive and convulsive rTMS, and may provide a new model for studies of epilepsy.

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The Mood-Lowering Effect of Tryptophan Depletion: Possible Explanation for Discrepant Findings

Tryptophan depletion (TD) is an experimental procedure for studying brain serotonin function. The mood-lowering effect of TD has been demonstrated in formerly depressed patients treated with selective serotonin reuptake inhibitors (SSRIs) or monoamine oxidase inhibitors[1] and in medication-free women with a history of recurrent depressive episodes.[2] Typically, a little more than half of the patients experience the effect. It is not exactly clear why some patients experience the effect while others do not. Several studies have recently found that the effect may be less consistent than previously thought. Moore et al[3] observed no effect on mood in fully remitted patients medicated with SSRIs. In a study[4] of patients who had responded to treatment with citalopram, only 5 of 12 patients relapsed, and the effect seemed to be clinically significant in only 1 patient. In a third study,[5] only 33% of 21 patients experienced a relapse. Moore et al[3] suggest that their unexpected finding may be related to sample differences. In comparison with earlier studies, their patients had been in treatment longer and were less depressed. Therefore, the effect of TD may be limited to recently recovered, medicated patients.[3] However, clinically significant symptom increases have been observed in euthymic patients who had not been receiving medications for at least 6months.[2] Another factor that might be involved is a patient's history of suicidal ideation.[6]

A simple explanation for the negative findings may be insufficient depletion. In Moore et al,[3] the mean reduction of free plasma tryptophan levels was 52%. This is lower than the typically reported 75% to 90% mean reduction. However, because this value was significantly different from the reduction in the placebo condition (5.6%), the authors consider their study successful in obtaining a contrast between TD and placebo conditions. However, the extent of depletion needed to achieve reliable mood effects has never been established. It cannot be ruled out, therefore, that there is a threshold that needs to be exceeded before an effect on mood occurs. Some indirect evidence supports this hypothesis. For instance, in the citalopram-responders study,[4] total plasma tryptophan reduction was also modest: 44.6% (free levels not reported). Furthermore, Delgado et al[1] found a significant negative correlation ($r=-0.60$) between minimum level of free tryptophan and depression score. Inspection of their Figure 4[1(p 415)] suggests that a nonlinear relationship is also possible. Ten of 12 patients with free tryptophan levels lower than or equal to 1 µmol/L had a relapse, compared with only 2 of 9 patients with a level greater than 1 µmol/L. In the study by Bremner et al,[5] tryptophan reductions were not statistically different between patients who relapsed and those who did not. However, with the threshold hypothesis in mind, the difference may be clinically significant. The reduction in free plasma tryptophan in the relapse group was 77.9%, compared with 57.5% in the no-relapse group. Finally, a recent study found that a 67% reduction of free tryptophan produced the expected worsening of depressive symptoms, whereas a 34% reduction did not.[7] These studies[5] suggest that the hypothesized threshold lies somewhere around a 60% reduction of free plasma tryptophan.[7] However, it may be that the hypothesized threshold should be defined in terms of the ratio between tryptophan level and large neutral amino acids (because these compete at the blood-brain barrier). In conclusion, the effect of TD on mood in formerly depressed patients may be more consistent than suggested by these negative findings. A reanalysis of large datasets may determine the relative contribution of extent of depletion, medication status, presence of suicidal ideation, and time since remission.

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In reply

Like many investigators, we have wondered why some but not all euthymic depressed patients treated with SSRIs or monoamine oxidase inhibitors (MAOIs) suffer a clinical relapse following rapid tryptophan depletion (RTD). Many clinical and behavioral measures vary widely between psychiatric patients and healthy volunteers with RTD, although plasma tryptophan reductions tend to be consistent and robust in both groups. Numerous attempts to correlate changes in plasma tryptophan scores with changes in depression scores or other measures have often failed to indicate a significant relationship.[1-10]

Dr Van der Does points out our lack of mood findings and smaller plasma tryptophan depletions compared with other reports.[2,11] These findings may be attributable to our depleting tryptophan in the afternoon and evening hours, when plasma tryptophan levels tend to peak,[12] and this may have had a blunting effect on plasma tryptophan depletion. However, even with these comparatively smaller depletions, each of the 10 remitted depressed patients treated with SSRIs showed significant effects on REM (rapid eye movement) sleep measures following both strengths (25 g and 100 g) of a tryptophan-depleting mixture. Therefore, although RTD did not induce depressive relapse in our patients, it did have measurable central nervous system effects consistent with depletion of serotonin. Similarly, in MAOI-treated depressed patients, RTD reversed the MAOI-induced suppression of REM sleep without depressive relapse.[13] Euthymic patients receiving SSRIs or MAOIs are more vulnerable to RTD-induced relapse early in treatment when they are in partial remission (Hamilton Rating Scale for Depression score, approximately 8-10 at 4-6 weeks) than later in treatment when they are in full remission (Hamilton Rating Scale for Depression score, approximately 3 at around 5 months).

How should depressive relapse be defined? According to the criteria of Delgado et al,[10] a 50% increase in Hamilton Rating Scale for Depression score constitutes relapse. Our remitted patients, for example, increased from 2 points to 3 (a 50% increase) on a modified Hamilton Rating Scale for Depression following RTD, but does this truly reflect clinical relapse? In our studies of depressed patients and normal volunteers, RTD elicited changes such as increased Confusion and decreased Vigor, Elation, and Friendliness in Profile of Mood States subscales. Whether the gap between these changes and depressive relapse is simply a matter of degree remains to be seen. Based on the literature and our own experience, we believe that true depressive relapse induced by RTD in SSRI and MAOI euthymia needs to be verified by other groups.

In contrast to our REM sleep findings in SSRI and MAOI-treated depressed patients, the RTD-induced REM sleep effects are less consistent in healthy volunteers,[1,2,14] despite consistent depletion of plasma tryptophan. In our reexamination of the data, the RTD-induced REM sleep measures in healthy volunteers show an almost dichotomous

effect: either a very pronounced REM-disinhibiting effect (such as an occurrence of sleep-onset REM) or virtually no effect. In this regard, we agree with Dr Van der Does regarding the notion of a "threshold" effect with RTD, but posit that it is not based in plasma, but located more centrally, such as in neuronal pools of serotonin.

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Did Samson Have Antisocial Personality Disorder?

Besides intrinsic, historical, and literary interest, and pedagogical utility, the study of the history of a disease can provide clues to its pathogenesis. It is necessary, but not sufficient, that the cause of disease be at least as old as the disease itself. We note a possible case of antisocial personality disorder (ASPD) nearly 3000 years ago: the biblical figure Samson (Judges,[1] chapters 13-16), son of Manoah.

The *DSM-IV* requires that 3 of 7 criteria be met for the diagnosis of ASPD. Samson meets 6. (1) Failure to conform to social norms with respect to lawful behavior: The Philistines tried to arrest Samson after he burned the Philistine fields (15:5) and went to Gaza (16:1). (2) Deceitfulness, as indicated by repeated lying: Samson did not tell his parents that he had killed a lion. Furthermore, he proffered honey for his parents to eat, but did not tell them it had come from the carcass of a lion (14:9) and thus caused them to violate their dietary laws. (3) Impulsivity: His burning of the Philistine fields (15:5). (4) Irritability and aggressiveness: This is indicated by his repeated involvement in physical fights. (5) Reckless disregard for safety of self or others: Samson is reported to have taken on and killed 1000 Philistines single-handedly (15:15). Telling Delilah the secret to his strength (16:17), even after she had attempted 3 times previously to get this secret, can also be considered reckless disregard for safety of self. (6) Lack of remorse: He gloated (15:16) after killing 1000 men.

In addition, Samson committed many of the actions listed in the criteria for conduct disorder—fire setting, cruelty to small animals (15:5), bullying, initiating physical fights, using a weapon (jawbone of ass) (15: 15), and stealing from a victim (14:19). If conduct disorder did not start when Samson was younger than 15 years, he was quite young (14:1-6).

Samson shows no evidence of schizophrenia. Some of his behaviors (eg, not telling his parents that the honey had been taken from a carcass) seem to have been done during a nonmanic state.

Samson's conduct was unacceptable in his time—3000 Israelites (Samson's own people!) captured Samson and delivered him to the Philistines (15:12).

Recognition of the diagnosis of ASPD for Samson may help in better understanding the biblical story, and, in general, may help in instances when a leader has ASPD. Also, we hope it stimulates interest in the history of ASPD.

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