TABLE 1. Risk of Suicide-Related Events During Periods of Lithium Treatment Compared With Periods Without Lithium Treatment in Patients With Bipolar Disorder Who Have Not Been Diagnosed With a Mixed Episode (2005–2013)

	Within-Individual Analysis[a]		Between-Individual Analysis[b]	
Patient Group	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Any bipolar disorder, excluding patients with mixed episodes[c]	0.82	0.73–0.93	0.80	0.72–0.89
Bipolar I disorder, excluding patients with mixed episodes	0.74	0.49–1.11	0.73	0.55–0.98
Bipolar II disorder, excluding patients with mixed episodes	0.55	0.38–0.80	0.73	0.53–0.99

[a] Stratified Cox regression was applied with adjustment for time-varying covariates including valproate treatment, age categories, and previous number of suicide attempts.
[b] Ordinary Cox regression was applied with adjustment for the same covariates as in the stratified Cox regression and, additionally, with adjustment for time-fixed covariates including sex, length of baseline hospitalization periods due to psychiatric admissions (a measure of illness severity), and history of suicide-related events before entering follow-up.
[c] This group includes all patients with bipolar disorder identified in the patient register regardless of subtype (i.e., including bipolar disorder not otherwise specified). The mixed episode was identified using ICD-10 (F316).

suggestion, the effect of lithium on the rate of suicide-related events increased in both bipolar I and bipolar II disorder when patients diagnosed with mixed episodes were excluded (1). However, the association remained nonsignificant for patients with bipolar I disorder. Two points should be noted, however. First, even though the patient register uses ICD-10 codes, many clinicians in Sweden used DSM-IV and translated diagnoses to ICD-10. In addition, DSM-IV requires that the criteria for both depression and mania be met (except the time criterion) in order to diagnose a mixed episode. This means that it is still possible that the bipolar I disorder group contains individuals with mixed features according to DSM-5. Thus, we cannot refute Dr. Terao and colleagues' suggestion. Future studies using DSM-5 criteria are needed to answer their question. Second, because ICD-10 does not distinguish between bipolar I and bipolar II disorder, we used data from a quality register for the subgroup analyses. This quality register contains only one-third of all Swedish patients with bipolar disorder, which decreases the size of the study sample. Thus, the fact that the results in bipolar I disorder do not reach statistical significance might be a power issue. Therefore, we agree with Terao et al. that more efforts are needed to explore the effect of lithium in preventing suicidal behavior in specific subgroups, where not only the subtype of bipolar disorder is taken into account, but also mixed features.

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Targeting Obsessive-Compulsive Symptoms With rTMS and Perfusion Imaging

TO THE EDITOR: In May 2015, a 27-year-old man was referred to our hospital because of treatment-resistant obsessive-compulsive disorder (OCD), from which he had suffered since age 12. He had undergone first-line treatment including cognitive-behavioral therapy together with different selective serotonin reuptake inhibitors (Figure 1A). However, despite adequate treatment dosages, OCD symptoms remained severe (Figure 1).

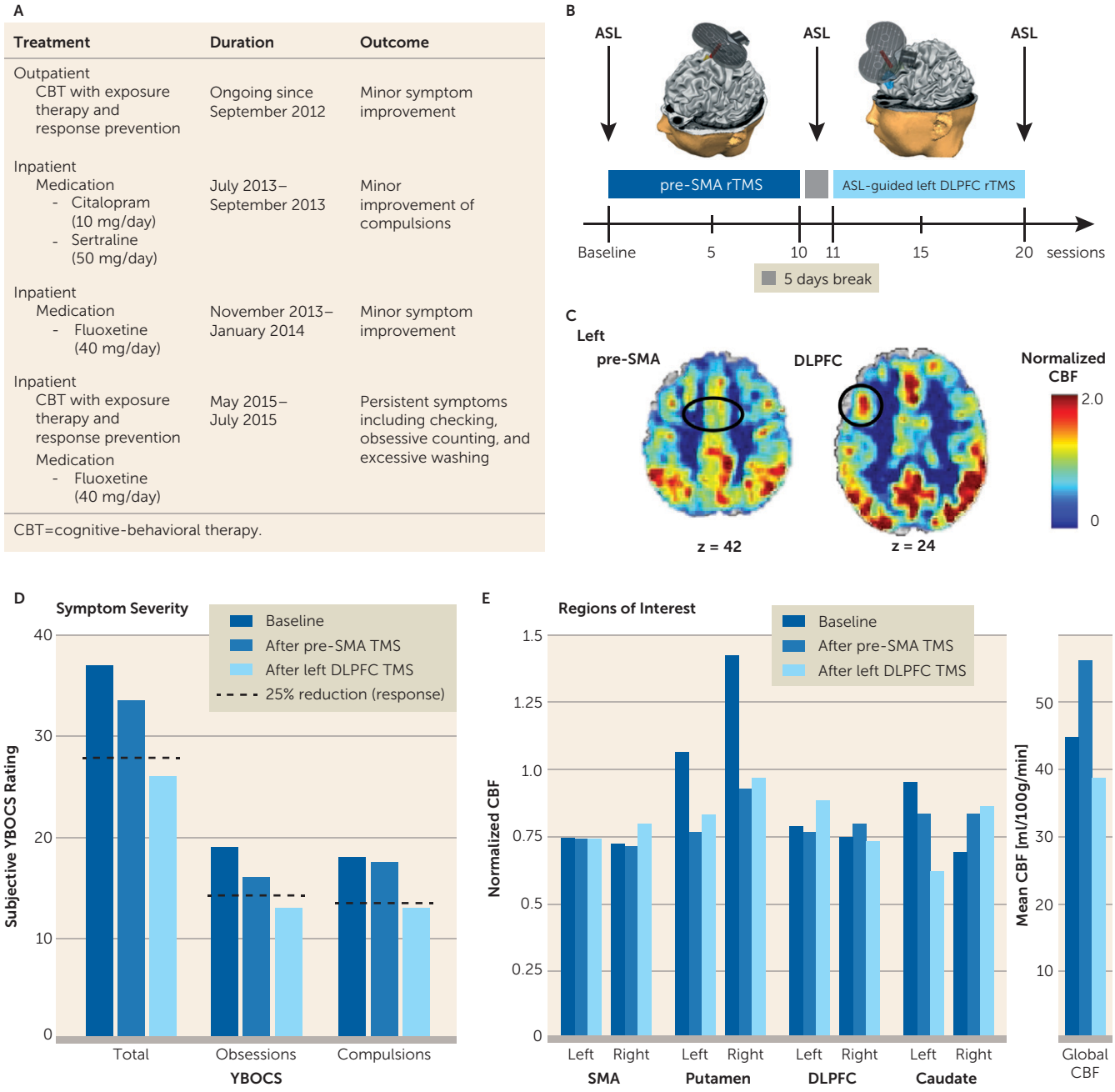
For augmentation purposes, repetitive transcranial magnetic stimulation (rTMS) has been suggested, although previous results concerning outcome, stimulation site, and TMS protocols have been inconsistent (2). In OCD, rTMS is administered to target cortical regions, such as the pre-supplementary motor area and the dorsolateral prefrontal cortex (DLPFC) (2), which are connected to hyperactive subcortical components of the cortico-striato-thalamo-cortical circuitry. Because most recent results of low-frequency rTMS over the presupplementary motor area have been promising (3), we stimulated this region for 10 sessions with a fluid-cooled 70-mm figure-8 coil and 1-Hz and 20-minute trains (1,200 pulses/day) at 100% of resting motor threshold. However, symptom reduction was only modest after the treatment (Figure 1D), and arterial spin labeling (ASL), a noninvasive neuroimaging technique that measures cerebral blood flow (CBF), revealed hyperperfusion in areas related to cortico-striato-thalamo-cortical circuitry such as the left DLPFC after rTMS of the presupplementary motor area. Therefore, another 10 sessions of rTMS were applied over the left DLPFC, a target region that also has shown promise in previous studies but has never been targeted using ASL-guided neuronavigation (2). In a second treatment series, we thus used ASL-guided rTMS over the left DLPFC allowing optimal localization and online monitoring

FIGURE 1. Effects of Repetitive Transcranial Magnetic Stimulation on Obsessive-Compulsive Symptoms and Cerebral Blood Flow[a]

A

Treatment	Duration	Outcome
Outpatient CBT with exposure therapy and response prevention	Ongoing since September 2012	Minor symptom improvement
Inpatient Medication - Citalopram (10 mg/day) - Sertraline (50 mg/day)	July 2013–September 2013	Minor improvement of compulsions
Inpatient Medication - Fluoxetine (40 mg/day)	November 2013–January 2014	Minor symptom improvement
Inpatient CBT with exposure therapy and response prevention Medication - Fluoxetine (40 mg/day)	May 2015–July 2015	Persistent symptoms including checking, obsessive counting, and excessive washing

CBT=cognitive-behavioral therapy.



[a] As shown in panel A, several first-line treatments failed to reduce symptoms of obsessive-compulsive disorder (OCD). As shown in panel B, we applied low-frequency repetitive transcranial magnetic stimulation (rTMS) over the bilateral presupplementary motor area once a day, 5 days per week for 2 weeks based on studies with promising results concerning OCD symptomatology. Panel C displays arterial spin labeling (ASL) measurements after presupplementary motor area rTMS revealed persistent hyperperfusion in the left dorsolateral prefrontal cortex (DLPFC) (Montreal Neurological Institute space). To focus on regional changes, we normalized cerebral blood flow (CBF) values by dividing them by the mean gray matter–corrected global CBF. As shown in panel D, symptom improvement was noted after the two rTMS treatments. As shown in panel E, assessments after left DLPFC rTMS revealed a more than 25% reduction of symptom severity (which is sometimes considered the clinical response criterion for the Yale-Brown Obsessive Compulsive Scale [YBOCS]) and CBF decrease especially in the left caudate nucleus, a part of the cortico-striato-thalamo-cortical circuitry. The slight regional CBF increase in the left DLPFC after rTMS over this particular area has been reported previously (1). One explanation for this potentially counterintuitive phenomenon is that the TMS-induced inhibition leads to a selective activity increase in inhibitory neurons that in turn causes the CBF increase under the coil, while activity in excitatory neurons decreases (1). SMA=supplementary motor area.

of the coil's position, applying the same stimulation parameters as in our first treatment. Medication remained stable the 2 weeks before and during the intervention. Assessment following left DLPFC rTMS showed a more convincing clinical reduction on the Yale-Brown Obsessive Compulsive Scale and CBF decrease in the left caudate nucleus, which is structurally connected to the left DLPFC. This result suggests a specific neurobiological effect of

rTMS especially over the left DLPFC on the cortico-striato-thalamo-cortical circuitry (Figure 1B through 1E).

To our knowledge, this case report, a retrospective analysis of rTMS treatment administered as part of routine clinical care, is the first to use ASL-guided rTMS over the left DLPFC in OCD. By providing a quantitative index of CBF during a brief and noninvasive resting state measurement, ASL might be well-suited for clinical applications involving rTMS. Although we found reduced symptom severity and CBF in OCD-related regions, we cannot rule out possible carry-on effects of the proceeding presupplementary motor area rTMS because of the uncontrolled design of the study. Therefore, further research is required to determine the optimal stimulation site and duration.

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CORRECTION

In the article "Complementary Features of Attention Bias Modification Therapy and Cognitive-Behavioral Therapy in Pediatric Anxiety Disorders" by Lauren K. White, Ph.D., et al. (Am J Psychiatry 2017; 174:775–784) there was an error in a data point for one patient in the placebo ABMT treatment condition. Data for this patient had not been included in the imaging analyses, but were included in the randomized controlled trial (RCT) analyses. When data for the subject are removed from the analyses, the PARS ratings for the placebo ABMT group reported in Table 2 change (pretreatment: mean=16.86 [SD=3.07]; midtreatment: mean=15.35 [SD=2.89]; posttreatment: mean=13.47 [SD=3.09]) as do the CGI-I scores (midtreatment: mean=4.29 [SD=0.64]; posttreatment: mean=3.33 [SD=0.96]). Removal of this subject also changes the primary RCT analysis of the posttreatment PARS ratings differences from p=0.04, Cohen's d=0.51 to p=0.07, Cohen's d=0.45.