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## Original Article

# Rapid switching of mood in families with familial bipolar disorder

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***Objective:*** Rapid switching of moods in bipolar disorder has been associated with early age at onset, panic comorbidity, and suicidality. This study aims to confirm these associations and investigate other potential correlates of rapid switching of mood using families from a multisite bipolar linkage study.

***Methods:*** The subjects were comprised of 1,143 probands and relatives with diagnosis of bipolar disorder. All subjects were interviewed directly with a standard diagnostic instrument, and all subjects who met criteria for bipolar disorder were asked if their moods had ever switched rapidly.

***Results:*** Individuals with rapid mood switching had significantly earlier age at onset (18 versus 21 years, $p < 0.00001$), higher comorbid anxiety (47% versus 26%, $p < 0.00001$) and substance use disorders (52% versus 42%, $p = 0.0006$), higher rate of violent behavior (6% versus 3%, $p < 0.004$), suicidal behavior (46% versus 31%, $p < 0.00001$), and nonsuicidal self-harm (13% versus 6%, $p < 0.0002$). Multiple logistic regression analysis found significant net effects on rapid mood switching for early emergence of symptoms [odds ratio (OR) = 0.62; 95% confidence interval (CI): 0.45–0.85]; anxiety comorbidity (OR = 2.31; 95% CI: 1.34–3.98); and hypersensitivity to antidepressants (OR = 2.05; 95% CI: 1.49–2.83) as the strongest predictors.

***Conclusions:*** This confirms earlier reports associating rapid switching with a more complex clinical course, in particular early emergence of bipolar symptomatology, antidepressant activation, and anxiety comorbidity. These results support a clinical differentiation of bipolar disorder into subtypes based on symptom stability.

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There is mounting evidence for multiple patterns of course, comobidity and clinical phenomenology consistent with the diagnosis of bipolar disorder (1–5). One pattern beginning to take shape is that of an early-onset, affectively unstable form of illness, in contrast to the classic concept of distinct, pervasive, opposing mood states of mania and depression (6–8). It is an open question whether these are common, subclinical expressions of manic-depressive experience, or represent a disorder similar in form to bipolar disorder, yet etiologically distinct.

On one hand, individuals who otherwise have classic manic and depressive syndromes often, at times, experience rapidly switching moods (9–11). On the other hand, rapid mood shifts and affective instability respond to different biological treatments (12, 13) consistent with evidence of distinct etiological factors (14, 15). It is also possible that

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the distinction between unstable and classic forms of manic-depressive illness is a distinction without a biological difference; perhaps the tendency to report rapid switching may derive from a hypersensitivity to one's internal states (neuroticism) which might also be a temperamental predisposition to anxiety, comorbidity, and behavior difficulties that could get the disorder diagnosed earlier in life. This alternative begs the question, however, of how much of a role these temperamental factors may play in the general risk for bipolar disorder.

The useful application of a concept of phenomenological heterogeneity based on course factors in bipolar disorder is limited by uncertainty about diagnostic boundaries, as illustrated above, but also by uncertainties in terminology. Affective instability in DSM-III could define both borderline personality and mixed bipolar states; in DSM-IV, one can assign the rapid cycling specifier to a bipolar disorder diagnosis when a person has sudden shifts in polarity, but only if the episodes last a week (for manic symptoms) or two (for depressive symptoms). Alternative terminologies have thus arisen to describe fluctuating affective states too brief to warrant a DSM bipolar disorder diagnosis, such as ultra-rapid and ultradian cycling (16, 17); however, these constructs also tend to assume not only sudden mood changes, but regular or cyclical changes. At a more basic level, a focus on the primary symptom of mood instability – the frequent fluctuations into and out of manic and depressive mood states – requires no such assumptions of cyclicity, and has been robustly associated in one study with a variety of clinical features such as earlier age at onset of bipolar disorder, greater comorbid anxiety, higher risks of suicide attempts and antidepressant-induced activation, and higher risk of having a relative with rapid switching (7). Therefore, one conclusion that can be drawn from this study (7) is that rapid switching of mood may form the core element of these phenomena of bipolar specifiers (rapid cycling, ultra-rapid cycling, ultra-ultra rapid, or mixed states), but may also be a unifying concept that links affective instability of temperaments to those of bipolar disorders.

Neurobiological research looking at the biological mechanisms of bipolar disorder has faced tremendous challenges resulting from the heterogeneity inherent in this syndrome. Some genetic studies have found an association between the rapid-switching forms of bipolar disorder, such as ultra-rapid (14), but not the common form, with a low-activity allele of the catecholamine-O-methyl transferase. Although such findings remain to be validated, these together with previous findings of elevated catecholamines in urine (18, 19) begin to converge towards a plausible biological mechanism.

The relative recency in the emergence of this form of expression of bipolar disorder in practice is potentially one of the reasons for the difficulty in validating rapid switching. It had been suggested (20) that rapid episode and mood shifts barely existed over two decades ago, and that their emergence may have been the result of secular trends in diagnosis, such as assigning more persons with mood instability to bipolar spectrum conditions rather than borderline personality disorder, and the increasing prescription of antidepressants and abuse of illicit drugs.

This replication analysis follows the same analytic method, applied to a larger set of individuals, interviewed with an updated version of the diagnostic interview in which some of the ambiguities in the earlier study have been worked out. Our primary focus here is to confirm whether this phenomenon of rapid switching has a consistent clinical implication in a different sample.

## Methods

### Participants

The participants for this study were ascertained through probands with assumed bipolar I disorder from 10 centers across the United States, as part of the National Institute of Mental Health (NIMH) Bipolar Disorder Genetics Initiative. Detailed description of the process of identification of participants, ascertainment and diagnoses has been described previously (21). Briefly, families were identified from local treatment facilities and various media outreach techniques by investigators from 10 participating sites: Indiana University (Indianapolis, IN), Johns Hopkins University (Baltimore, MD), Rush Presbyterian Medical Center (Chicago, IL), University of California at Irvine (Irvine, CA), University of California at San Diego (La Jolla, CA), University of Chicago (Chicago, IL), University of Iowa (Iowa City, IA), University of Pennsylvania (Philadelphia, PA), Washington University (St. Louis, MO), and the NIMH Intramural Research Program (Bethesda, MD). Informed consents were approved by the Institutional Review Boards of the various institutions, and each participant was administered an informed consent before receiving any study procedure. The families were ascertained on the basis of having a proband with a diagnosis of bipolar I (BPI) affective disorder and at least one sibling affected with BPI or schizoaffective disorder, bipolar type (SABP). Subjects were

interviewed by use of the Diagnostic Interview for Genetic Studies (DIGS) (22), which has been shown to exhibit excellent test–retest reliability for the diagnosis of affective disorders. Final assignment of a bipolar disorder diagnosis, using DSM-IV criteria, was the result of a best-estimate process in which trained diagnosticians consulted the DIGS, as well as data gathered using the Family Interview for Genetic Studies (FIGS) and relevant medical records, when available. Diagnoses were made by consensus or, when the two raters disagreed, by a third rater. Data on rapid switching were derived from the mania section of the DIGS. All subjects completing the section were asked: 'Have you ever switched back and forth quickly between feeling high and feeling normal or depressed?' Affirmative answers were followed by a request to specify the frequency of the mood switch. For this analysis, rapid switching of mood was defined by affirmative answer to the first question irrespective of the frequency of mood switching.

### Statistical analysis

From the multi-site data set, 2,006 study participants completed the mania section. Of those who completed the mania section, 1,287 met the criteria for bipolar disorder or SABP. (Subjects with hypomania were excluded if they had only one depressive episode.) A total of 1,145 subjects provided sufficient information on mood switching. Two other subjects had insufficient record of their manic episodes and age at onset, and were dropped from the final sample. Of the remaining 1,143 subjects, 1,029 (90%), 77 (7%), and 37 (3%) met criteria for bipolar I, bipolar II, and schizoaffective disorder, bipolar type, respectively.

The STATA statistical software (Stata Corporation, College Station, TX, USA) was used for all analyses. Variables with $>10\%$ missing information were not used in the final analysis. Since the minimum requirement for inclusion in this analysis was information on mood switching, there were no missing data on the primary outcome measure. An extra dummy category was created for missing categorical variable values, and median values of known data were used to impute missing continuous values.

To determine familiality of rapid switching of mood, we included data on the risk that any given subject had a relative who also reported experiencing rapid switching of mood. We included the latter for reporting and for use in regression analysis. As the family size of the entire sample was variable, ranging from one to eight members, and also included arbitrary ranges of relatedness, we subsequently tested for familiality within first-degree relatives in informative families (i.e., families of size of at least two members). By permutation, we randomly generated unrelated probands with rapid switching and unrelated controls without rapid switching and calculated the relative odds of rapid switching in their family members. A total of 364 case-control probands provided informative family history of rapid switching.

For the goal of estimating the relative utility of rapid mood switching as a core factor in the clinical heterogeneity of these subjects, compared with the DSM-IV rapid cycling specifier, we derived the DSM-IV rapid cycling variable from the data set. The subjects who completed the mania section were asked: 'Have you had a year when you had several different manic, hypomanic, depressive, or mixed episodes?' Those who gave affirmative answers were asked to report the number of episodes they had in that one year, and whether there was recovery between episodes. For this study, DSM-IV rapid cycling was defined as having at least four episodes of mood disturbance in a year, with each episode demarcated by recovery, or without recovery if there is a shift from one mood polarity to an opposite polarity. A total of 251 (44%) of the 568 subjects with a lifetime report of rapid switching also had history of rapid cycling. To evaluate familial risk for rapid cycling, we applied a similar technique as was used to analyze familial rapid switching.

Participants' self-reports on demographic features, such as age, race, marital status, etc., were used for our analyses. To determine antidepressant-associated activation, we accepted the categorical answer to the question: 'Did you ever feel high or were you overactive following medical treatment for depression?' For clinical features and course specifiers, such as age at onset, age of first treatment, and number and duration of episodes, the final best-estimate report of these features made by investigators at each center, were used for this analysis. Similarly, the consensus diagnoses for comorbid psychiatric conditions, such as anxiety disorders, substance abuse, eating disorders, etc., were used for the logistic regressions, as the diagnosticians based their diagnoses of these psychiatric comorbidities on the DSM-IV operational criteria. For general medical conditions, including histories of hypothyroidism and migraine, self-report of a physician's diagnosis was coded. For instance, on the question of migraine the participants were asked: 'Has a doctor ever told you that you had migraine?' Those who answered affirmatively were asked to provide additional description of the migraine symptoms. Only those who had a

physician's diagnosis and corresponding description were included as affected by the medical condition in question for inclusion in bivariate and multivariate logistic regression.

Group differences in categorical variables such as gender and comorbid conditions were explored using simple tabulations, and odd ratios (OR) between each group were generated using simple logistic regressions with associated 95% confidence interval (CI) and p-values. For continuous variables, we evaluated for patterns of distribution between the rapid switching groups by using simple stem-and-leaf plots and box plots. Since variables of interest such as age at onset of bipolar disorder, age at first outpatient treatment, episodes of mania/hypomania, and duration in weeks of the longest depression showed non-normal patterns, we used nonparametric Mann–Whitney tests to obtain p-values for between-group differences. We dichotomized age at onset at 15 years mainly for the purpose of the finding in an earlier study (7), which showed a very strong effect of age at onset $<15$ years (OR = 7.14; $p < 0.001$) in a bivariate analysis of rapid switching of mood. In addition, 15 years was the modal age at onset for subjects with rapid cycling, and the distribution of age at onset is unimodal in our entire sample. To determine predictors of rapid mood switching, we used an initial logistic regression model of all 32 candidate clinical variables available in the data set.

To account for within-family member correlations in both bivariate and multivariate analyses, generalized estimating equations (GEE) were used (23). Briefly, GEE are methods of parameter estimation for correlated data, such as observations from members within and between families. These methods derive robust estimates of standard errors, making hypothesis of parameter estimates in such correlated data sets more valid (23). A backward stepwise selection procedure using $p = 0.05$ for deletion was used to derive the final model. Odd ratios and p-values with significance defined as $p < 0.05$ were reported in our results. Female sex and family history, though statistically insignificant at the set threshold, were included because of presumed clinical significance. We investigated the possibility of interaction effects among the clinical variables, but none were found to be both statistically significant and clinically meaningful. The final model fit the data according to the Hosmer–Lemeshow goodness-of-fit test ($p = 0.7630$). Here a high p-value supports a good fit.

Finally, to explore which of these clinical characteristics in probands best predict rapid switching of mood in relatives, we conducted logistic regressions treating family history as the outcome variable, accounting for correlation of variables with robust variance techniques using STATA.

## Results

There were a total of 1,143 subjects with diagnosis of bipolar disorders, from 533 families. The mean family size was 2.55 members and the range was 1–8. Almost half of the 1,143 subjects with the diagnosis of bipolar disorder who provided any information on rapid switching answered affirmatively that they had experienced rapid switching of mood. Table 1 shows the demographic characteristics stratified by rapid switching. Those with rapid switching differed in gender, marital status, highest educational achievement and age at interview. The rapid switching group had more females, less tendency to be married/widowed and lower educational attainment both as continuous and as a categorical measure. Subjects with rapid switching were also more likely to have a relative reporting rapid switching in the interview (62% versus 49%). Individuals with rapid switching were also younger at the time of the interview.

Individuals with and without rapid switching did not differ significantly in the categorical subtypes of bipolar disorder (Table 1). However, there is a positive correlation between rapid switching and meeting the DSM-IV classification of rapid cycling (Spearman coefficient of 0.4, $p < 0.0004$). Forty-four percent of relatives with rapid switching of mood met the operational construct for rapid cycling, compared to 12% of relatives without rapid switching (OR = 5.71; 95% CI: 4.20–7.82). Subjects with rapid switching had significantly more episodes of mania and hypomania, compared to those without rapid switching. Individuals with rapid switching had an (estimated) mean [interquartile range (IQR)] of five episodes (2–20) versus three (1–7.5) in the non-rapid switching individuals ($Z$-statistic = $-6.48$; $p < 0.00001$). Individuals with rapid switching had a lower age at onset of first manic or depressive episodes—(estimated) mean (SD) years of 18 (7.8) versus 21 (8.9) ($p < 0.00001$), and as such had lower mean age at first outpatient treatment, 22.4 versus 23.5 years old. Relatives with rapid switching had a nearly threefold higher risk of being diagnosed with childhood hyperactivity/learning disorder (11% versus 4%), and a twofold higher risk of reporting antidepressant-induced activation (36% versus 18%). Both groups appear similar in the rate of psychosis.

Rates of substance use and psychiatric comorbidities are 1.5 to 3.4 times higher in the rapid

Table 1. Demographic, clinical characteristics and comorbid conditions in family members with bipolar disorder with and without rapid switching of mood

| Characteristic | Rapid switching (n = 568) | Non-rapid switching (n = 575) | OR (95% CI)[a] | p-value[b] |
|---|---|---|---|---|
| Relative with rapid switching, n (%) | 354 (62) | 283 (49) | 1.71 (1.34–2.18) | |
| Female, n (%) | 387 (68) | 361 (61) | 1.32 (1.04–1.71) | |
| Marital status, n (%) | | | | |
| Never married | 175 (31) | 155 (27) | 1.00 | |
| Married/widowed | 248 (44) | 288 (50) | 0.76 (0.57–1.01) | |
| Separated/divorced | 145 (26) | 132 (23) | 0.97 (0.70–1.36) | |
| Education level, n (%) | | | | |
| High school or less | 180 (32) | 135 (23) | 1.00 | |
| Some college or graduated | 294 (52) | 304 (53) | 0.73 (0.55–0.96) | |
| Beyond college | 94 (17) | 136 (24) | 0.52 (0.36–0.74) | |
| Age at interview, years, mean (SD) | 39.9 (11.3) | 44 (12.3) | | <0.0001 |
| Education, years, mean (SD) | 14.3 (2.75) | 14.9 (2.82) | | <0.0003 |
| Bipolar disorder subdiagnosis, n (%) | | | | |
| Bipolar II disorder | 33 (6) | 44 (8) | 1.00 | |
| Schizoaffective, bipolar type | 20 (4) | 17 (3) | 1.57 (0.66–3.73) | |
| Bipolar I disorder | 515 (91) | 514 (89) | 1.34 (0.82–2.20) | |
| Rapid cycling, n (%) | 251 (44) | 104 (12) | 5.71 (4.20–7.82) | |
| Psychosis with affective episode, n (%) | 286 (50) | 271 (47) | 1.14 (0.90–1.44) | |
| Antidepressant-associated high, n (%) | 204 (36) | 104 (18) | 2.54 (1.92–3.37) | |
| Childhood learning disorder/hyperactivity, n (%) | 64 (11) | 24 (4) | 2.92 (1.77–4.95) | |
| Episodes of mania, median (interquartile range) | 5 (2–20) | 3 (1–7.5) | | <0.0001[c] |
| Age at onset of bipolar disorder, years, mean (SD) | 18 (7.81) | 21.0 (8.87) | | <0.0001 |
| Age at first outpatient treatment, years, mean (SD) | 22.4 (9.12) | 23.5 (9.86) | | <0.05 |
| **Comorbid disorders** | | | | |
| Anxiety disorders, n (%) | | | | |
| Obsessive-compulsive disorder | 61 (11) | 20 (3) | 3.38 (1.95–5.92) | |
| Panic disorder | 184 (32) | 100 (17) | 2.27 (1.71–3.04) | |
| Social phobia, simple phobia, or agoraphobia | 122 (21) | 77 (13) | 1.77 (1.28–2.45) | |
| Any anxiety disorder | 265 (47) | 152 (26) | 2.43 (1.88–3.14) | |
| Substance abuse or dependence, n (%) | | | | |
| Alcohol abuse or dependence | 249 (44) | 200 (35) | 1.46 (1.14–1.87) | |
| Cocaine/amphetamine abuse or dependence | 87 (15) | 57 (11) | 1.64 (1.13–2.39) | |
| Any substance abuse or dependence | 297 (52) | 242 (42) | 1.51 (1.19–1.92) | |
| Any drug abuse or dependence | 194 (34) | 132 (23) | 1.74 (1.33–2.28) | |
| Eating disorder, n (%) | | | | |
| Anorexia | 19 (3) | 13 (2) | 1.62 (0.74–3.70) | |
| Bulimia | 37 (6) | 14 (2) | 2.79 (1.45–5.65) | |
| Hypothyroidism, n (%) | 32 (6) | 20 (3) | 1.66 (0.91–3.10) | |
| Migraine, n (%) | 118 (21) | 70 (12) | 2.28 (1.59–3.16) | |
| Head injury, n (%) | 198 (35) | 153 (26) | 1.51 (1.17–1.96) | |

OR = odds ratio; CI = confidence interval.
[a]OR: ratio of the odds of being a rapid switcher for those with the characteristic compared to those without the characteristic or those in the reference category.
[b]p-values from Student's *t*-tests, unless otherwise stated; only p-values significant at <0.05 level are shown.
[c]p-values from Mann–Whitney nonparametric test; only p-values significant at <0.05 level are shown.

switching individuals (Table 1). Statistically, the most significant difference was seen with obsessive-compulsive disorder (OCD) (11% versus 3%; OR = 3.38). While the difference in bulimia was significant (OR = 2.79; 95% CI: 1.45–5.65), no significant difference was seen in anorexia. Individuals with rapid switching also had higher rates of recurrent migraine and history of head injuries: 21% versus 12%, and 35% versus 26%, respectively.

Rates of suicide attempts, self-injurious behavior and violence were also compared (Table 2). Participants that endorsed rapid switching had a 1.9 (95% CI: 1.47–2.42) times higher rates of suicide attempt, a 2.14 (95% CI: 1.39–3.34) times higher rates of self-injury, and a 2.36 (1.26–4.62) higher rate of irritability-related violence, compared to individuals without rapid switching. The mean rates of suicide attempts were also higher in those with rapid switching, 1.31 versus 0.84 ($p < 0.0001$).

Table 2. Suicide attempts, self-harm, and violent behavior in 1,143 family members with bipolar disorder with and without rapid mood switching

| | Rapid switching (n = 568) | No rapid switching (n = 575) | OR (95% CI)[a] | p-value[b] |
|---|---|---|---|---|
| Ever attempted suicide, n (%) | 259 (46) | 177 (31) | 1.88 (1.47–2.42) | <0.0001 |
| Suicide attempts, mean (SD) | 1.31 (2.42) | 0.84 (2.78) | | <0.0001[c] |
| Self-harm without suicide intent, n (%) | 73 (13) | 37 (6) | 2.14 (1.39–3.34) | <0.0002 |
| Ever violent when irritable, n (%) | 36 (6) | 16 (3) | 2.36 (1.26–4.62) | <0.004 |

OR = odds ratio; CI = confidence interval.
[a]OR: ratio of the odds of being a rapid switcher for those with the characteristic compared to those without the characteristic or those in the reference category.
[b]p-values from Wald test, unless otherwise stated; only p-values significant at <0.05 level are shown.
[c]p-values from Mann–Whitney nonparametric test; only p-values significant at <0.05 level are shown.

Table 3. Logistic regression analysis of potential risk factors for rapid mood switching in 1,143 family members with bipolar disorder

| Characteristic[a] | Odds ratio (95% CI) | p-value |
|---|---|---|
| **Demographic** | | |
| Female | 1.21 (0.91–1.63) | <0.20 |
| Relative with rapid switching | 1.37 (0.92–1.88) | <0.08 |
| Age at bipolar onset >15 years | 0.62 (0.45–0.85) | <0.004 |
| **Psychiatric comorbidity** | | |
| Panic disorder with agoraphobia | 1.74 (1.10–2.76) | <0.05 |
| Obsessive-compulsive disorder | 2.31 (1.34–3.98) | <0.003 |
| Childhood hyperactivity/ learning disorder | 2.00 (1.16–3.44) | <0.02 |
| Suicide attempts | 1.35 (1.02–1.81) | <0.04 |
| **Medical comorbidity** | | |
| Hypothyroidism | 2.10 (1.12–3.93) | <0.03 |
| Migraine history | 1.33 (1.10–1.61) | <0.004 |
| Head injury | 1.27 (1.04–1.54) | <0.02 |
| Activation by antidepressants | 2.05 (1.49–2.83) | <0.001 |

CI = confidence interval.
[a]The logistic regression controlled for race, education, and any substance abuse or dependence and included any additional risk factors from Table 1 using backwards variable selection procedure.

The results of the logistic regression of rapid switching on clinical characteristics collected in the study are shown in Table 3. Adjusting for other clinical variables in the model, history of antidepressant-induced activation remained significant (OR = 2.05; 95% CI: 1.49–2.83; $p < 0.001$). Categorically, age at onset >15 years old also showed inverse association with rapid switching, reducing the odds for rapid switching by 38%. There was a two times higher risk of rapid switching given a diagnosis of obsessive-compulsive disorder, hypothyroidism or a childhood diagnosis of hyperactivity or learning disorder. Histories of head injury, panic disorder with agoraphobia, suicide attempts, and recurrent migraine remained significant predictors of rapid switching, and increased the odds for rapid switching between 1.2 and 1.7 times. Though the age at interview of bipolar disorder has been shown to be significantly lower in the individuals who endorsed rapid switching, it had a lower impact in the odds for rapid switching (OR = 0.97; 95% CI: 0.96–0.98) in the adjusted model. Longest episode of depression in weeks and age at first treatment also resulted in weak associations in our best model. Gender and family history of rapid switching did not significantly affect the risk for rapid switching.

From further analysis of familiality (data not shown) in 364 unrelated case-control probands using only first-degree relatives, family history of familiality of rapid switching was present in 60% of probands who endorsed rapid switching, compared with 43% positive family history in probands without rapid switching (OR = 1.95; 95% CI: 1.24–2.04). Furthermore, clinical characteristics in probands that best predict family history of rapid switching include, in order of effect size and significance: childhood history of hyperactivity/learning disorder (OR = 2.24; $p = 0.001$); panic disorders (OR = 2.11; $p < 0.001$); age at onset (as a continuous variable) (OR = 0.96; $p < 0.001$); substance abuse or dependence (OR = 1.62; $p < 0.001$); and history of migraine (OR = 1.62; $p = 0.008$). Though proband's history of repeated self-injurious behaviors showed a trend in association (OR = 1.35; $p = 0.06$), proband's reported suicide attempt did not show significant association with familial rapid switching of mood [OR = 1.20 (n.s.)].

## Discussion

In this large, multisite study of families with multiple members diagnosed with bipolar disorder, a high proportion of participants indicated that they had experienced rapid switching of mood. The parent study is a genetic study of bipolar disorder, with a family design. Therefore, we have a data set of families for our analysis and utilized the function of GEE in STATA to handle correlated

observations. Our results add to evidence (7, 24) that a positive self-report to this one interview item defines a distinct subset of bipolar disease with significant variation in age at onset and other psychiatric and nonpsychiatric comorbidities. Further, this study replicates some of the significant risk factors associated with rapid switching, such as age at onset and antidepressant activation, but also goes further in depth in testing the robustness of these associations by adjusting for other important clinical risk factors. We will examine these associations first, and later discuss their significance. The large sample size also allowed us to test for interactions, results of which are not shown because they were insignificant in the regression model.

Previous reports have supported association between panic disorder and rapid switching or rapid cycling. It has been reported in some studies that rapid switching (or cycling) and panic disorder aggregates in some families (24–27). In this study, while the broad group of panic disorder is seen as associated with rapid switching, only panic disorder with agoraphobia remained significant after adjusting for age, gender, and variables in our model. The odds for rapid switching increased nearly twofold in a model unadjusted for family history of rapid switching. This implies that family history of rapid switching may explain some of the association between panic disorders and rapid switching, suggesting a common genetic risk in some families for both conditions. Interestingly, the strong association between another anxiety disorder, OCD, and rapid switching may lend clinical credence to genetic association studies looking at shared vulnerability for OCD, panic disorder, and some impulse-control disorders. One report showed that a functional variant in the promoter region of the serotonin transporter gene (5HTTLPR) is associated with OCD, panic disorder, and some impulsive disorders (28). This gene may be a potential candidate in the causation of anxiety disorders and rapid switching in some families.

This study opens a perspective into the possible relationship between childhood hyperactivity, with or without learning disorders, and later diagnosis of bipolar disorder with rapid switching. Whether this indicates diagnostic confusion between attention-deficit hyperactivity disorder (ADHD) and childhood bipolar disorder, or suggests that ADHD may be a prodromal form of bipolar disorder, remains an open question. Our interview instrument only asked participants if they were diagnosed with childhood hyperactivity by their doctor, but did not include specific questions on symptom criteria for ADHD. With this limitation in mind, we cannot confidently equate the hyperactivity reported by our participants with definite ADHD. We therefore can only speculate regarding a specific relationship between bipolar disorder and ADHD, and leave open the important question of how to handle the differential diagnoses of mood lability and hyperactivity in child and adolescent age groups (29–31).

In this study, we were able to estimate and test for association between medical conditions such as hypothyroidism, migraine, and head injury with rapid switching. Results of studies testing the relationship between hypothyroidism and rapid cycling or rapid switching have been conflicting; some results (32, 33) report significantly increased risk of rapid switching in subjects with hypothyroidism, while others (34, 35) report either a weak association or none. A meta-analysis of various publications, however, supported an effect of hypothyroidism in a subset of people (36). In our earlier analysis of rapid switching (7), we found no association with self-reported hypothyroidism; however, in this study we used doctor-diagnosed hypothyroidism and examined data on medication use to confirm that subjects had indeed received thyroid replacements as further validation of an actual diagnosis. The relationship between hypothyroidism and rapid switching is poorly known, but we speculate that it may reflect increased sensitivity of susceptible subjects to homeostatic changes and even external environmental agents. The same can be said of migraine association. Incidentally, several reports (37–39) have linked recurrent migraine history with rapid cycling, and moreover, some anticonvulsant medications used successfully as migraine prophylaxis have been equally effective in the management of rapid switching in patients diagnosed with bipolar disorder (40). The relationship between head injury and rapid switching is poorly understood. Small clinical studies and case reports have shown that head injuries have been associated with later onset of bipolar disorders. However, we also know that subjects with a diagnosis of bipolar disorder are prone to accidents due to highly impulsive behaviors, such as reckless driving.

We have replicated the previously reported finding of familiality of rapid switching. Restricting our analysis to first-degree relatives of probands with bipolar disorder, we found a nearly twofold increase in the risk for rapid switching among bipolar-diagnosed family members of probands with rapid switching. We cannot, however, confirm, based on this analysis, whether the source of familiality is a specific genetic subtype of bipolar

disorder, the presence of a distinct genetic trait that modifies illness course in bipolar disorder, or perhaps environmental factors. The utility of our finding of familiality in the risk for rapid switching is in its support of biological studies of bipolar disorder that take into account course variables such as age at onset (41), psychosis (42, 43), and polarity at illness onset (44), to mention but a few.

This study further supports an earlier result demonstrating that a categorical response to this one question about rapid switching provides consistent predictions on course, severity and comorbidities associated with bipolar disorder. Although this question has not been widely validated and would not explain the entire concept of episodic frequency and rapid mood shifts, it is remarkable that the findings converge with those of rapid cycling in our data and in other studies (7). More importantly, the question of whether one has ever switched back and forth quickly between feeling high to feeling normal or depressed has been relatively easy to ask. Though we did not obtain item-by-item test of reliability for questions in the mood section of the interview, we have obtained excellent test–retest reliability of the affective diagnosis with this diagnostic instrument (45). The differentiation of rapid switching as a state of bipolar disorder from issues of unstable temperament may be examined prospectively by application to patients in unstable mood states, of frequent serial mood and symptom ratings for both mania and depression. Most standardized mood assessments, such as the Young Mania Rating Scale (46) and Montgomery-Asberg Rating Scale (47), gather data over periods of time longer than the cycle of rapid switching and would be less useful. It would be particularly interesting to investigate the association of documented frequent mood shifts with the results of a temperament assessment such as the NEO-Personality Inventory (48, 49).

Instruments to measure personality and temperamental traits were not obtained in this study; therefore, we have no direct information as to how individuals endorsing rapid switching compare with persons who would be considered to have Cluster B traits. It is worth remembering, however, that even if there is an overlap in the concepts of rapid switching and unstable personality (50), our subjects with rapid switching, whether or not they could be diagnosed with something like borderline personality disorder, all were confidently diagnosed with bipolar disorder. The retrospective nature of the study, and the vulnerability within this methodology to apply diagnostic concepts *post hoc* to clinical phenomena, point to the need for prospective research to validate these findings.

The replication and extension of the association of rapid switching in bipolar disorder with a number of specific variables in bipolar disorder phenomenology further supports the hypothesis that rapid switching is a core component of a bipolar disorder subtype characterized by affective instability, early age at onset, anxiety comorbidity, and behavioral impulsivity. Information on past treatment was rudimentary and subject to recall bias, and so was not helpful in assessing the relationship of treatment and rapid switching. As this study and the study it replicates were conducted in families collected for bipolar disorder linkage study, it remains to be seen whether these findings are applicable to the wider population of individuals with (apparently) nonfamilial bipolar disorder. A population-based study would likely be required to answer this question; however, ascertainment of the rapid switching phenomenon in large clinical trial samples might be a more practical means of validating these findings.

The idea that some individuals with bipolar disorder experience greater flux than others in their episode frequency and rate of switching is not so much new as it is a potential refinement of concepts variously described in the DSM and the literature as mixed states, ultra-rapid cycling, and affective lability. The implications of this hypothesis for the enhancement of therapeutic strategies and for the understanding of disease etiology remain to be seen.

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