

Brief Report

MMPI as a measure of subthreshold and residual psychopathology among the offspring of lithium responsive and non-responsive bipolar parents

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Objectives: In bipolar adults, the Minnesota Multiphasic Personality Inventory (MMPI) can detect residual symptoms and confirm completeness of remission, thus helping to predict response to lithium prophylaxis. In the high-risk and early onset bipolar populations, the association of the MMPI with clinical course and treatment response has not yet been studied. The present study compares MMPI profiles completed by the well or remitted offspring of two groups of bipolar parents divided on the basis of parental response to long-term lithium.

Methods: As part of an ongoing prospective longitudinal high-risk study, offspring of bipolar parents determined to either respond or not respond to long-term lithium monotherapy completed the MMPI. At the time of MMPI completion, offspring were determined to be either well (unaffected) or clinically remitted (affected but euthymic) based on repeated prospective KSADS-PL format interviews conducted by a research psychiatrist and reviewed on a blind consensus basis.

Results: While there was no difference in the MMPI scores between subgroups of unaffected offspring, there was a significant difference in profiles between remitted offspring. Specifically, affected offspring of lithium non-responders showed significantly higher average scores on scales 6, 8 and 0 compared with affected offspring of lithium responders. These findings are consistent with the differences in MMPI profiles taken at optimum between the respective parent subgroups.

Conclusions: The findings confirm the clinical observation that the affected offspring of lithium responders suffer from episodic fully remitting mood disorders, while the affected offspring of lithium non-responders suffer from mood disorders with incomplete remission. Further, the nature of the residual symptoms as indicated by the abnormal MMPIs support the view of heterogeneity of the bipolar diagnosis. The relevance to treatment response is discussed.

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Bipolar disorder is an increasingly heterogeneous diagnostic category (1, 2) and subtypes can be

identified on the basis of clinical characteristics including clinical course, family history of psychopathology and long-term response to lithium treatment (elimination of recurrences on lithium, despite a high recurrence risk before lithium) (3–5). Responders to lithium prophylaxis (referred to as LiRs) typically experience a recurrent remitting

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clinical course, and have other family members with recurrent mood disorders, not schizophrenia. During the free interval in adult bipolar LiRs, there is no psychopathology detectable either on clinical interview or psychological testing (6). In fact, in remission LiRs show normal Minnesota Multiphasic Personality Inventory (MMPI) profiles. In contrast, bipolar probands who do not respond to long-term lithium characteristically experience a non-episodic course of illness, and have family members with psychotic spectrum and anxiety disorders (7, 8). The MMPI profiles of non-responders to lithium prophylaxis (refer to as LiNRs) taken at optimum show abnormalities indicative of residual symptomatology. Specifically, there are characteristic elevations of scales 6 and 8 and/or 1, 3 and 0, which are consistent with psychotic features, anxiety symptoms, and social introversion, respectively.

Subgroup differentiation within the bipolar spectrum is largely based on historical information about the clinical course, treatment response and family history. The ability to differentiate, at least partially, on a cross-sectional measure such as the MMPI would be very helpful. As well, the nature of the MMPI during the free interval appears to be a useful predictor of long-term treatment response (6, 9, 10). Therefore, we sought to study the MMPI-2/A (adult and adolescent) profiles of the offspring of LiR and LiNR bipolar parents at their optimum level of functioning (unaffected and well or affected but in clinical remission). We hypothesized that the offspring of LiRs would themselves show a normal MMPI profile at their optimum, while the offspring of LiNRs would show abnormal profiles suggestive of residual psychopathology. Further, we hypothesized that the nature of these residual symptoms would be comparable with that of the LiNR parents; namely, elevations on scales 6, 8, 1, 3 and 0. This study is part of a larger ongoing prospective longitudinal high-risk study comparing the offspring of LiR and LiNR bipolar parents previously reported (11, 12).

Method

Bipolar parents

Proband parents met DSM-IV criteria for bipolar I disorder on the basis of Schedule of Affective Disorders and Schizophrenia – Lifetime Version (SADS-L) interviews and consensus diagnosis using all available clinical information. Lithium response was determined in accordance with research protocol described in previous publica-

tions (4). In summary, lithium response was decided on the basis of a highly recurrent course prior to lithium and no recurrences of mood episodes on adequate lithium monotherapy (based on a blood level ≥ 0.7 mmol/L) for a minimum of 3 years. Lithium non-response was determined on the basis of at least two recurrences on adequate lithium treatment (based on blood levels ≥ 0.7 mmol/L at the time of relapse). Parents were described in detail elsewhere (13), as part of ongoing genetic studies. These parents completed MMPI-2 when determined to be clinically remitted or stabilized on treatment (Clinical Global Impression Scale – Severity of Illness, CGI-S ≤ 2 ; normal or borderline severity of residual symptoms) based on prospective clinical assessment. For the high-risk study, families were included only if the other parent (non-bipolar parent) had no lifetime history of a recurrent mood disorder (unipolar or bipolar), anxiety disorder, psychotic spectrum illness or substance use disorder.

Subjects

As part of an ongoing prospective longitudinal high-risk study (12), 53 consenting offspring of identified bipolar parents (described above), aged 8–25 years, were clinically assessed using the Schedule of Affective Disorders and Schizophrenia for school-aged children – Present and Lifetime Version (K-SADS-PL) interview format conducted by the principal investigator (AD) at enrolment, annually and at anytime symptoms developed. All available clinical and research information was reviewed on blind consensus basis by at least two independent research psychiatrists, one being a child and adolescent subspecialist. For this report, all consenting high-risk offspring at least 13 years of age completed MMPI profiles (MMPI-A, adolescent version age 13–17; MMPI-2, adult version from age 18). Offspring ranged in age, 13–31 years, with most (over 60%) of the offspring falling between the ages of 17 and 24 at the time of testing. The median age at time of testing was 21.0 years for offspring of LiRs, and 19.5 years for the offspring of LiNRs. The mean duration of prospective study follow-up was 5.5 years (ranging from 7 to 97 months).

For this study, offspring completed the MMPI when they were deemed to be at their optimum based on prospective clinical assessment and defined as well (unaffected to date), in clinical remission (no significant residual symptoms causing either impairment or distress) or clinically stabilized on treatment (CGI-S ≤ 2). Ethics boards at the Royal Ottawa Hospital and the Queen

Elizabeth – II Hospital approved this study in accordance with their guidelines for the ethical treatment of research participants (REB #2003-15).

Measures

Measures included the MMPI-A (adolescent version), a revision of the original MMPI specifically designed for use with adolescent samples, and the MMPI-2 (adult version). The MMPI-A/2 self-report measures are typically used in hospital and outpatient clinics to measure general psychopathology and distress. The MMPI-A consists of 478 true/false items comprising seven validity scales (VRIN, TRIN, F, F₁, F₂, K and L) and 10 basic clinical scales (1 = Hs, 2 = D, 3 = Hy, 4 = Pd, 5 = Mf, 6 = Pa, 7 = Pt, 8 = Sc, 9 = Ma and 0 = Si), and the MMPI-2 consists of 567 true/false items comprising six validity scales (VRIN, TRIN, Cannot Say, L, F and K) and 10 basic clinical scales. Based on guidelines specified in the MMPI-A manual (14), offspring under 18 years of age were asked to complete the MMPI-A version, whereas proband parents and offspring over 18 completed the adult version of the measure (MMPI-2). The two MMPI versions have several similarities. First, both MMPI versions are comparable in terms of the clinical constructs they measure (i.e. basic clinical scales). Secondly, both have comparable measures of validity. Finally, many of the individual items are the same, and others have been rephrased to be more appropriate for youth samples. Any MMPI-2/A profile with a clinical scale T-score of 65 or higher was considered to be an abnormal profile.

Statistical analyses

A 2 (parental lithium response: response versus non-response to lithium) by 3 (affected status of offspring: mood disorder versus other Axis I disorder versus unaffected) factorial analysis of variance was used to calculate two main effects and an interaction effect using 10 MMPI-A/2 scales (F, 1, 2, 3, 4, 6, 7, 8, 9 and 0) as dependent variables. Of the total sample, 15 (28.3%) offspring completed the MMPI-A version of the instrument and 38 (71.7%) offspring completed the MMPI-2.

The MMPI-2 and MMPI-A scores were analysed together in the analyses for the following reasons: both versions of the instrument measure the same constructs and clinical psychopathology, thus in this case it is quite acceptable to analyse the scores together although they are based on disparate normative groups. In addition, for the purposes

of accuracy, it was important to include T-scores for both adult and adolescent versions that were relative to their age-appropriate norms. Finally, the distribution of MMPI-A measures completed in the LiR and LiNR offspring groups were comparable (i.e. the variance for the MMPI-A sample was comparable with the variance for the MMPI-2 sample).

Results

Descriptive statistics

Bipolar proband parents. This report includes the offspring of 13 (52%) LiRs and 12 (48%) LiNRs. The LiRs had a mean number of lifetime mood episodes prior to stabilization on lithium of 8.9 (SD = 7.0; ranging from three to 28 episodes) and 53.8% of LiRs were hospitalized during an episode within their lifetime. In comparison, the LiNRs had a mean duration of illness of 20.9 years and 66.7% of LiNRs were hospitalized during an episode within their lifetime. The mean number of episodes is not provided for the LiNR group given that they typically have a chronic course of illness and discrete episodes are difficult to reliably identify.

Offspring. Fifty-three offspring of bipolar probands were included in the analyses: 31 (58.5%) offspring were from LiR families and 22 (41.5%) were from LiNR families. The mean age of the sample at MMPI completion was 20.5 years (SD = 4.3). There were 21 male (39.6%) and 32 female (60.4%) participants. The mean ages and sex ratio were comparable across the high-risk subgroups. In addition, mean ages were comparable between the affected (21.4 ± 4.3 years), and unaffected (19.5 ± 4.1 years) groups, $t(51) = 1.7$, $p = \text{n.s.}$ Although there were more females in the affected group ($n = 21$) compared with the unaffected group ($n = 11$), there were no significant differences in sex ratios between the LiR and LiNR groups across affected status, thus all four subgroups were comparable (for affected offspring – Pearson chi-square: $\chi^2(1) = 0.68$, $p = \text{n.s.}$; for unaffected offspring – Pearson chi-square: $\chi^2(1) = 0.28$, $p = \text{n.s.}$).

Twenty-nine offspring (54.7%) met DSM-IV criteria for a previous lifetime Axis I psychiatric diagnosis. The majority of affected offspring met lifetime criteria for a mood disorder ($n = 21$; 72.4%) and eight (27.6%) offspring meet criteria for another Axis I disorder. The breakdown of primary psychiatric diagnoses for all offspring are detailed in Table 1. Of the LiR offspring, none of

Table 1. DSM-IV primary psychiatric diagnoses for offspring sample

| | Lithium responder offspring | Lithium non-responder offspring |
|---|-----------------------------|---------------------------------|
| Bipolar I | 2 | 0 |
| Bipolar II | 0 | 0 |
| Bipolar NOS | 2 | 1 |
| Dysthymia | 0 | 0 |
| Depression NOS | 2 | 2 |
| Major depressive episode | 0 | 3 |
| Recurrent major depression | 3 | 6 |
| Anxiety disorder | 4 | 0 |
| Substance abuse | 1 | 0 |
| Other (i.e. Learning disability, Adjustment disorder, ADHD) | 0 | 3 |
| Total affected | 14 | 15 |

those with primary mood disorders had comorbid anxiety disorders. However, of the 12 LiNR offspring with primary mood disorders, seven (58.3%) met diagnostic criteria for a comorbid anxiety disorder [i.e. Generalized Anxiety Disorder (GAD) or Anxiety Disorder NOS].

Despite a previous history of psychiatric disorder for 29 of the offspring, the majority of offspring were not on medication at the time of completing the MMPI (69.8%). Of those on medication for their illness, 10 (18.9%) were treated with antidepressants, three (5.7%) were treated with lithium, two (3.8%) were treated with atypical antipsychotics and one (1.9%) was treated with an anticonvulsant. There was no difference in the proportion of abnormal versus normal profiles between those on medication and those not on medication at the time of testing; namely, being treated with medication was independent of whether or not one had an abnormal profile on the MMPI-A/2 – Pearson chi-square: $\chi^2(1) = 3.4$, n.s.

Primary analyses. Parent MMPI data included here forms part of a larger study investigating MMPI profiles in remitted adult bipolar patients (unpublished data). The proportion of normal and abnormal profiles in the subgroups of remitted parents was analysed (see Table 2). There was a significantly increased number of abnormal profiles (i.e. profiles with a clinical scale T-score elevation of 65 or greater) among LiNR parents compared

Table 2. Proportion of lithium responsive and non-responsive parents with normal and abnormal profiles

| | LiR parents | LiNR parents |
|------------------|-------------|--------------|
| Normal profile | 10 (76.9%) | 1 (8.3%) |
| Abnormal profile | 3 (23.1%) | 11 (91.6%) |

$p = 0.001$.

Table 3. Affected and well offspring of bipolar parents: breakdown of normal versus abnormal MMPI-A/2 profiles

| | LiR offspring | | LiNR offspring | |
|----------|----------------|------------------|----------------|------------------|
| | Normal profile | Abnormal profile | Normal profile | Abnormal profile |
| Affected | 12 (38.7) | 3 (9.7) | 4 (18.2) | 10 (45.5) |
| Well | 15 (48.4) | 1 (3.2) | 5 (22.7) | 3 (13.6) |

Values in parentheses represent percentage.
 $p = 0.005$.

with LiR parents when tested at optimum – Pearson chi-square: $\chi^2(1) = 11.9$, $p = 0.001$. The abnormal parent profiles in this sample characteristically showed elevations on scales F, 2, 3, 6 and 0. The proportion of normal versus abnormal MMPI-A/2 for the offspring of these bipolar parents are detailed in Table 3, and also show a higher proportion of abnormal profiles among affected LiNR offspring compared with affected LiR offspring when completed at optimum. Namely, the Pearson chi-square showed that parental lithium response was related to profile type (normal or abnormal), $\chi^2(1) = 7.7$, $p = 0.005$.

An analysis of the offspring data using multivariate 2 by 3 factorial design was completed using parental lithium response (main effect A: lithium response or lithium non-response) and affected status of offspring (main effect B: primary mood disorder, other Axis I disorder, or unaffected) variables. The multivariate main effect for parental lithium response was not significant, Wilks' Lambda: $F(10,38) = 1.5$, n.s. A multivariate main effect for affected status of offspring was found, Wilks' Lambda: $F(20,76) = 2.1$, $p = 0.011$, however it is more comprehensively understood by examining the results of the interaction analysis. Based on specific a priori hypotheses, the univariate tests for the interaction term (parental lithium response \times affected status of offspring) were calculated. The univariate tests showed that for scales 6 and 8, there were significant differences between groups of LiR and LiNR offspring that were dependent on the affected status of the offspring, $F(2,47) = 6.5$, $p = 0.003$ and $F(2,47) = 3.8$, $p = 0.030$, respectively. There was a trend towards a significant difference between groups on scale F that was dependent on the affected status of offspring, $F(2,47) = 2.8$, $p = 0.070$. Follow-up simple main effect analyses revealed that among offspring affected with a mood disorder, offspring from LiNR families had significantly higher mean scores on scales 6 ($X = 61.9$, $SD = 8.7$), 8 ($X = 66.1$, $SD = 15.0$) and 0 ($X = 53.8$, $SD = 10.3$) than offspring from LiR families (scale 6: $X = 52.2$,

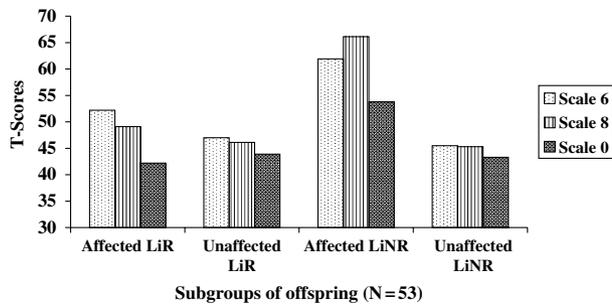


Fig. 1. Mean T-scores on scales 6, 8 and 0 of the MMPI-A/-2 for affected (with mood disorder) and unaffected offspring of lithium responsive and non-responsive bipolar parent probands.

SD = 7.4; scale 8: $X = 49.1$, $SD = 10.6$; scale 0: $X = 42.2$, $SD = 12.8$ [scale 6: $F(1,19) = 7.3$, $p = 0.014$; scale 8: $F(1,19) = 8.4$, $p = 0.009$; scale 0: $F(1,19) = 5.2$, $p = 0.034$] (see Fig. 1). A trend towards significant differences between the above two groups was found for scales 1, $F(1,19) = 4.0$, $p = 0.061$, scale 3, $F(1,19) = 3.6$, $p = 0.074$, and scale 7, $F(1,19) = 3.7$, $p = 0.069$, in the predicted direction. Namely, LiNR offspring with mood disorders had higher mean scores than LiR offspring with mood disorders for scales 1 (LiNR: $X = 63.9$, $SD = 12.8$; LiR: $X = 51.6$, $SD = 15.6$), 3 (LiNR: $X = 60.7$, $SD = 10.2$; LiR: $X = 52.1$, $SD = 10.4$) and 7 (LiNR: $X = 64.1$, $SD = 16.2$; LiR: $X = 51.7$, $SD = 12.2$). Within the group of offspring diagnosed with other Axis I disorders, LiR offspring scored significantly higher on scale 6 ($X = 52.7$, $SD = 8.5$) than LiNR offspring ($X = 37.0$, $SD = 2.8$), $F(1,6) = 6.0$, $p = 0.050$. Within the unaffected offspring, no differences emerged between offspring of LiR and LiNR parents.

Discussion

This study supported the hypothesis that affected offspring of LiRs would show normal MMPI profiles when completed in clinical remission, while the affected offspring of LiNRs would show abnormal MMPI profiles. Further, the nature of the differences in scale scores between the high-risk groups was consistent with the differences in the parent subgroup profiles. This suggests that even relatively early in the course of illness, clinical course characteristics (quality of remission) are consistent between generations and can be characterized on psychological testing. This is important, as an MMPI taken at optimum in the early onset population may not only represent the subtype of bipolar illness (classical versus non-classical), but may also predict responsiveness to lithium. That is, the complete remission on both clinical interview

and psychological testing among the affected offspring of LiRs suggests that they will do well on long-term lithium monotherapy. The incomplete remission and the nature of the residual symptoms among the affected LiNR offspring suggests that they will not do well on long-term lithium and in conjunction with other clinical characteristics such as premorbid functioning, clinical course and their family history may predict for long-term response to either lamotrigine or an atypical neuroleptic (5).

Among offspring of LiNRs with mood disorders, elevations on scales 6, 8 and 0 indicate residual symptomatology associated with the psychotic spectrum of symptoms as well as a tendency towards greater social introversion. Specifically, moderate elevations on scale 6 have been associated with rigid thinking, suspiciousness, and interpersonal sensitivity. Scale 8 measures psychotic-related symptoms, poor judgement, unconventional thought or behaviour, possible overvalued ideas, feelings of isolation and alienation, and perceived lack of acceptance by others (14). Scale 0 measures social introversion; interpersonal sensitivity; and characteristics associated with being reserved and shy; overcontrolled and inhibited; serious, reliable and conventional; and compliant and submissive (14). Moreover, the trends that were found suggesting higher scores on scales 1, 3 and 7 for offspring of LiNR with primary mood disorders suggests the possibility of more residual anxiety symptomatology in this subgroup. This is a particularly interesting finding considering that the majority of LiNR offspring with primary mood disorders also met diagnostic criteria for a comorbid anxiety disorder such as GAD or Anxiety Disorder NOS. Moreover, these findings are consistent with the speculation that the bipolar diagnosis is a broad diagnostic category that captures a number of different illnesses. Some of the DSM bipolar disorders may be more related to psychotic spectrum disorders and some may be more related to anxiety-characterological disorders. This speculation has support in convergent findings from clinical course, family history and treatment response studies (15) and is consistent with the findings here. Recognizing valid subtypes within the bipolar spectrum is important because the majority of these patients should be able to be either fully remitted or well stabilized in the long-term on the appropriate treatment (5) and alternatively are at risk for poor outcomes if not optimally treated.

There are some clear limitations in this study. First, the sample size was limited and trends for differences on scales 1, 3 and 7 between affected

members of the two high-risk subgroups may have reached significance with a larger sample size. As well, the study involved one MMPI at optimum, and it would be most interesting to have prospective repeated data within individuals to compare premorbid MMPI profiles with those taken in remission after the onset of illness. Further, the majority of the psychiatrically affected offspring met DSM criteria for some form of mood or anxiety disorder, mostly depression. Estimates of the likelihood of latent bipolar disorder among first-degree depressed relatives of bipolar patients are in the order of 80% (16). Also, in our prospective study, we have reported that anxiety and depressive disorders are often antecedents to bipolar disorder in the high-risk population. Therefore, we feel the MMPI profiles represent a characterization of the remitted course in the early onset bipolar population. Finally, the samples of offspring affected with other Axis I disorders was quite small and would have to be increased for further analyses to be completed. In fact, it is possible that the higher score on scale 6 among the offspring of LiR parents with other psychiatric disorders was due to the small sample. The cases within the latter subgroup may have been outliers to some extent, and are likely not representative of the group as a whole.

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