Stroop-test interference in bipolar disorder

Eugenia Kravariti, Katja Schulze, Fergus Kane, Sridevi Kalidindi, Elvira Bramon, Muriel Walshe, Nicolette Marshall, Mei-Hua Hall, Anna Georgiades, Colm McDonald and Robin M. Murray

Summary
We analysed Stroop (neuropsychological screening test) measures of response inhibition in 18 twin pairs discordant for bipolar I disorder compared with 17 healthy control pairs, as well as 40 singletons with bipolar disorder with psychotic features and a family history of psychosis, 46 of their first-degree relatives without bipolar disorder or psychosis and 48 controls. In both studies, individuals with bipolar disorder showed Stroop deficits and their first-degree relatives showed intact performance. In the twin patients, an interference score was associated with depressive symptoms. Having a first-degree relative with bipolar disorder, even a familial, psychotic form, did not confer risk for enhanced susceptibility to interference in our studies.

Declaration of interest
None. Funding detailed in Acknowledgements.

A trait-related dysfunction in the ventral prefrontal cortex in bipolar I disorder has been proposed to underlie deficits in the effortful inhibition of pre-potent cognitive responses in favour of less automatic ones. Response inhibition deficits can be detected using neuropsychological screening tests such as the Stroop paradigm. Impairment in the latter showed the second largest effect size in relatives of bipolar probands in a recent meta-analysis, showing considerable promise as a candidate endophenotype. However, due to the paucity of relevant studies (n=4), and the substantial heterogeneity of effect sizes (0.00–1.03), this possibility needs further investigation.

We report Stroop findings from a study of twin pairs discordant for bipolar I disorder, and a study of singletons with bipolar disorder and their first-degree relatives without bipolar disorder or psychosis from families multiply affected with psychosis. Of the restricted number of neuropsychological measures that overlapped in the two studies, Stroop was selected for analysis due to its appeal as a candidate endophenotype. Relatives in both studies were presumed to have enhanced risk for carrying bipolar susceptibility genes owing to increased genetic overlap with an affected proband (56% of the twin pairs were identical) or to increased familial loading for functional psychosis. We predicted that patients and relatives in each study would show deficits compared with controls and the performance of relatives would fall in-between those of affected probands and controls.

Method

The two studies were conducted at the Institute of Psychiatry between 1999 and 2007 using non-overlapping samples. Main sources of recruitment were referrals from consultant psychiatrists across the UK, user-led organisations for people affected by bipolar disorder and local/national press advertisements. All participants were characterised diagnostically according to DSM–IV criteria. Structured diagnostic interviews using the Schedules for Clinical Assessment in Neuropsychiatry (twin study) and the Schedule for Affective Disorders and Schizophrenia – Lifetime Version (family study) were performed with all participants. Medical notes were also consulted for most patients. Information regarding psychiatric diagnoses of family members not directly assessed in the family study was obtained from reliable informants using the Family Interview for Genetic Studies and, when available, from psychiatric notes. All participants were native speakers of English and had no history of neurological disorder, organic brain disease or head trauma resulting in loss of consciousness for more than 10 min. Controls with personal/family histories of psychotic, bipolar or schizophrenia-spectrum disorders (up to second-degree relatives) were excluded from both studies. The twin study further excluded controls with any lifetime psychiatric diagnoses. No participant was acutely ill at testing (47% of probands obtained normal-range scores in the Beck Depression Inventory (1–9) and Altman Self-Rating Mania Scale1 (1–5) or had been alcohol or substance dependent over the 12 months preceding assessment (except one co-twin who was alcohol dependent). The Institute of Psychiatry’s ethical committee approved both studies.

Eighteen twin pairs discordant for bipolar I disorder and 17 healthy control pairs participated in the twin study. The family study included 40 patients with bipolar I disorder who had both a history of delusions or hallucinations during illness exacerbation and one or more first- or second-degree relative(s) with bipolar disorder or other functional psychosis. The study further included 46 of the patients’ first-degree relatives who had no personal history of psychotic, bipolar or schizophrenia-spectrum disorders, and 48 unrelated control participants. The descriptive characteristics of the studies and the demographic, clinical and neuropsychological characteristics of their respective samples are summarised in online Table DS1.

The Stroop4 was administered to all participants, yielding a colour-word score (number correct in the colour-word condition) and an interference score (number correct in the colour condition minus number correct in the colour-word condition). An alternative interference score (colour-word completion time minus colour completion time) was further estimated in the twin study.

In each study, group differences in Stroop scores were investigated in a series of two-step linear regressions for clustered observations, using robust standard errors to safeguard against potential violations of the standard ANOVA assumptions. In the first step, socio-demographic/IQ variables that had shown significant group differences in separate clustered regressions (twin study: age and IQ; family study: no differences emerged) were included in the models. In the second step, affective scores that had shown significant group differences in separate clustered regressions (twin study: depression score; family study: depression and mania scores) were further added to the models.

To examine whether controls with lifetime psychiatric diagnoses (family study only) or dizygotic discordant pairs ‘diluted’ the pattern of findings, all analyses were repeated after excluding both subgroups.

Linear regressions with robust standard errors were used to examine associations between Stroop performance and illness
duration/affective symptoms in the total patient sample of each study. Age was included as covariate in the twin-study model, because it emerged as a significant predictor of interference score ($P<0.01$) in the first-step analysis (described above).

Results
In both studies, significant or trend deficits were detected in the bipolar probands compared with co-twins/first-degree relatives, who were indistinguishable from controls, and in the family-study/monozygotic probands compared with controls (independent of control sample composition in the family study) (online Table DS1). After covarying for affective symptoms, twin probands (full sample) and monozygotic probands no longer showed trend deficits compared with co-twins/controls, but the remaining differences remained significant or were reduced to trends (online Table DS1). Depression significantly predicted ‘colour-word completion time minus colour completion time’ in the twin patients (coefficient=2.82, 95% CI 1.18–4.46, $P=0.002$).

Discussion
We report findings from a twin study, and the largest family study to date, investigating Stroop deficits in bipolar I disorder. The majority of co-twins without bipolar disorder were genetically identical with an affected proband, while the relatives of the family study came from families with multiple occurrences of functional psychosis. Both studies were ideally suited to detect inhibitory control deficits in individuals at presumed enhanced risk for carrying bipolar susceptibility genes. The large sample size, strict statistical control for socio-demographic and intellectual confounders, and combination of two powerful study designs are unique strengths of the present investigation.

Both studies found increased susceptibility to interference in patients with bipolar disorder and intact inhibitory control in their first-degree relatives. The twin study further showed an association between depression and an interference score. Corroborating two earlier studies,14,15 these findings do not support our hypothesis that increased susceptibility to interference is an endophenotype for bipolar I disorder.

Most studies of response inhibition in patients with euthymic bipolar disorder16–18 and relatives of probands15,19 have ascertained index cases through specialist clinical settings. A notable difference of our study is its broader source of ascertainment. In addition to the usual routes, affected probands were identified through user-led organisations and press advertisements. It is, therefore, possible that a familial risk for enhanced susceptibility to interference is confined to a subgroup of patients, who are more likely to be found among in-patient and out-patient cohorts.20

Our findings do not rule out the possibility that trait-related dysfunction in neural substrates of inhibitory control coexists with intact Stroop performance in individuals at risk for bipolar I disorder.1,2

We conclude that being a first-degree relative of an individual with bipolar I disorder, even a severe form with psychotic features and increased familial loading, does not necessarily confer risk for enhanced susceptibility to interference.

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7 Wing JK, Babor T, Brugha T, Burke J, Cooper JE, Giel R, et al. SCAN. Schedules for Clinical Assessment in Neuropsychiatry. Arch Gen Psychiatry 1990; 47: 589–93.
Our study involved assessing the impact of various factors on cognitive performance using the Wechsler Abbreviated Scale of Intelligence (WASI) in both twins and family studies. We collected demographic, clinical, and neuropsychological data to understand the relationships between these variables. Here’s a summary:

### Demographic and Clinical Characteristics
- **Gender:**
  - Twins: Male = 8, Female = 8
  - Controls: Male = 14, Female = 14
- **Age at Testing:**
  - Twins: Mean (SD) = 13.8 (10.2), 25 (11.1), 22
  - Controls: Mean (SD) = 14 (14.3)
  
### Neuropsychological Characteristics
- **Stroop Completion Time:**
  - Twins: Mean (SD) = 15.2 (4.0), 21.9 (4.1), 18.8 (4.2)
  - Controls: Mean (SD) = 16.3 (3.2), 21.9 (4.1), 18.8 (4.2)

### Additional Notes
- **Medication:**
  - Mood stabilisers: 38 of the controls had no lifetime psychiatric diagnoses.
- **Wechsler Abbreviated Scale of Intelligence (WASI):**
  - Full-Scale IQ: Mean (SD) = 112.5 (8.9), 114.8 (9.0), 119.5 (9.9), 110.6 (14.4), 113.6 (11.6), 115.1 (9.8)

### References
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