Eur Arch Psychiatry Clin Neurosci (2012) 262:125–130
DOI 10.1007/s00406-011-0213-7

ORIGINAL PAPER

Dissociable and common deficits in inhibitory control in schizophrenia and bipolar disorder

Tessa Christodoulou · Lambros Messinis · Panagiotis Papathanasopoulos · Sophia Frangou

Received: 15 December 2010 / Accepted: 7 April 2011 / Published online: 22 April 2011

Abstract Current research focuses on delineating the neurobiological boundaries between familial risk for schizophrenia (SZ) and bipolar disorder (BD). Available evidence suggests that inhibitory control may be affected in both disorders. Inhibitory control relies on the dual processes of contextual information maintenance and response inhibition. This study investigated the effect of familial risk of SZ or BD on these two aspects of inhibitory control. Seventeen healthy first-degree relatives of patients with BD (BD-R), 15 healthy relatives of patients with SZ (SZ-R) and 23 demographically matched controls were compared in terms of their performance during Controlled Oral Word Association (COWA), which measures contextually driven response selection, and during the Hayling Sentence Completion Test (HSCT), which assesses contextual response selection and inhibition. Compared to controls and BD-R, SZ-R showed deficits in contextual information processing that resulted in spontaneous errors in the COWA as well as deficits in response inhibition during the HSCT that resulted in higher error rates. BD-R also showed deficits in response inhibition during the HSCT relative to controls, which were, however, less pronounced than for SZ-R. Both relatives groups had longer response times. Our results suggest that failure in contextual maintenance is primarily associated with familial risk for SZ, while response inhibition may be a shared marker of familial risk for both disorders.

Keywords Cognition · Inhibitory control · Verbal fluency · Response inhibition · Schizophrenia · Bipolar · First-degree relatives

T. Christodoulou (✉) · S. Frangou
Section of Neurobiology of Psychosis, Institute of Psychiatry, King's College London, P066, De Crespigny Park, Denmark Hill, London SE5 8AF, UK
e-mail: tessa_christodoulou@hotmail.com

L. Messinis · P. Papathanasopoulos
Department of Neurology, Neuropsychology Section, University of Patras Medical School, Rion, Patras, Greece

Introduction

Schizophrenia (SZ) and bipolar disorder (BD) are currently considered separate nosological entities [1]. However, there is significant evidence of an overlap primary in terms of genetic aetiology [23]. Much research effort is currently focused on delineating the neurobiological boundaries between the two disorders using cognitive test performance as a probe. A number of meta-analyses have compared the cognitive profile of patients with SZ or BD [4, 5, 25, 32, 42]. The general consensus is that the two disorders differ in terms of general intellectual quotient (IQ), which appears preserved in BD but is significantly impaired in SZ, while deficits in memory, attention and aspects of executive function are present in both disorders. However, within these wide cognitive domains, there is increasing evidence for further disease specificity, particularly in inhibitory control. Inhibitory control is a multifaceted concept that incorporates aspects of cognitive and behavioural control in connection to selective attention, appropriate (i.e. contextual) action selection and response inhibition and performance monitoring [2]. Here, we focus on the processes of maintaining contextual information (e.g. task rules) and selecting an appropriate response over other alternatives.

A common task for assessing inhibitory control is the Stroop Colour Word Test (SCWT) [18, 43], which requires

individuals to withhold an overlearned but inappropriate verbal response in favour of the appropriate one. In our recent meta-analysis comparing patients with SZ with those with BD or major depressive disorder (MDD), we found that impairment in the SCWT was associated with mood disorders rather than SZ. Deficits in response inhibition in the SCWT have been reported in unaffected relatives of BD patients [3, 5], suggesting that this cognitive function is also related to familial risk for the disorder. SZ patients show more generalised deficits in verbal responding during the SCWT, which suggests that the core problem is not in response inhibition per se but in the inefficient contextual modulation of language-processing pathways [16]. Further support for this notion derives from studies using tests of verbal fluency that assess the ability to generate task appropriate responses but have no explicit inhibitory requirement. Patients with SZ not only generate fewer contextually appropriate words than controls but they also have a high rate of errors; they persevere or provide contextually inappropriate words. These verbal fluency deficits are one of the most robust findings in SZ research affecting both patients [25] and their relatives [21, 40, 44]. In contrast, verbal fluency abnormalities in BD patients consist of reduced word production rather than in errors, and even then the effect size compared to controls is small [29, 37, 39, 46] and becomes negligible when comparing controls to unaffected relatives [3, 5, 12, 31]. Taken together, these findings suggest that familial risk for SZ maybe associated with deficits ascribed to poor inhibitory control may reflect inefficient maintenance of contextual set while familial predisposition for BD may be linked to inadequate control of response inhibition.

In order to explore this hypothesis, we compared test performance in the Controlled Oral Word Association test (COWA) [41] and in the Hayling Sentence Completion Test (HCST) [6] in healthy first-degree relatives of patients with SZ or BD. COWA is a verbal fluency task that involves the generation of words based on letter cues. The HSCT has two conditions: the initiation condition also involves generation of words based on sentence cues, while the inhibition condition requires participants to suppress a semantically predicted word in favour of a contextually unrelated word. The HSCT has been successfully used in studies of SZ and BD [15, 50] although not as widely as the SCWT. However, this test is better suited for this study design because it is purely language based, while the SCWT has a significant perceptual attention component. We examined healthy relatives of patients with either BD or SZ as our focus was on familial influences on neuropsychological performance. Additionally, this design avoids potential confounds of medication or psychopathology. We hypothesised that (a) both in the COWA and the initiation condition of the HSCT, relatives of patients with BD (BD-R) will be able to maintain contextual set, while relatives of patients with SZ (SZ-R) will underperform compared to BD-R and controls, (b) both BD-R and SZ-R will show impairment in the inhibition condition of the HSCT compared to controls. We also hypothesised that if inhibitory errors in SZ reflect poor maintenance of contextual set then the number of errors in the COWA in SZ-R (but not BD-R) would predict errors in HSCT.

Methods

Participants

Seventeen first-degree relatives of patients with BD (BD-R), fifteen first-degree relatives of patients with SZ (SZ-R) and 23 demographically matched healthy controls (HC) were drawn from participants enrolled in two ongoing departmental studies [1, 14, 17, 24, 26, 27, 34–36, 45, 48]. Relatives were sampled from different families and were therefore unrelated. Ethical approval was obtained from the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee. Written informed consent was obtained from all participants.

For this analysis, we only included relatives without any current or lifetime personal history of any Axis I disorder based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) [1]. Similarly controls were free of any personal or family history (up to second degree) of Axis I disorders. Exclusion criteria for all participants included (a) head trauma resulting in loss of consciousness, (b) personal history of neurological or medical disorders, (c) family history of hereditary neurological disorders, and (d) drug or alcohol abuse in the preceding 6 months as defined by the DSM-IV. Level of education was rated on a 5-point scale ranging from 1 (no educational qualification), 2 ("O" levels), 3 ("A" levels), 4 (university degree or equivalent) to 5 (postgraduate university level qualifications).

Procedure

Clinical assessment

All participants (relatives and controls) underwent the same diagnostic assessment using the Structured Clinical Interview for DSM-IV Axis I Disorders [13] administered by trained psychiatrists. Family history was assessed using Family Interview for Genetic Studies (FIGS) [30]. Psychopathology was further assessed on the day of their cognitive testing with the Brief Psychiatric Rating Scale (BPRS) [47], the 21-item Hamilton Depression Rating

Scale (HDRS) [19] and the Young Mania Rating Scale (YMRS) [51].

Neuropsychological assessment

All participants were tested by the same psychologist (TC). Tests were administered in a single session. The HSCT comprises two conditions each of which has 15 different sentences each with the last word missing. Each sentence is read to participants who are required to provide the missing word. In the initiation condition, participants are required to complete the sentence with a word predicted by the context (e.g. He posted the letter with a _ STAMP). In the inhibition condition, participants are asked to provide a totally unconnected word (e.g. The captain wanted to stay with the sinking _ BANANA); category A errors occur when participants provide a contextual predicted word (e.g. the captain wanted to stay with the sinking _ ship) and category B errors when they provide a semantically related word (e.g. the captain wanted to stay with the sinking _ sea). Performance in the HSCT is assessed in terms of response initiation time in each condition (i.e. time taken to provide a response) and response inhibition (i.e. number of category A and B errors).

In the COWA participants are asked to generate as many words as they can that begin with the letters *F*, *A*, and *S* in the 1960s. Performance is assessed in terms of total correct responses and total errors defined as the sum of intrusions and perseverations. Intrusions and perseverations are rule violations (non-words and proper nouns) and repetitions of words, respectively.

We used the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [49] Vocabulary subtest to obtain an estimate of current full-scale intelligence quotient (FSIQ). The test requires giving brief and precise definitions to concrete and abstract words presented in the order of increasing difficulty.

Statistical analysis

The three groups (SZ-R, BD-R and HC) were compared in terms of demographic characteristics and psychopathology scores using analysis of variance or chi-square tests as appropriate.

Outcome measures from the HSCT and COWA were entered as dependent variables in two separate multivariate analyses of covariance (MANOVA) with group as the independent factor, BPRS and FSIQ scores as covariates. We used raw scores rather than age-corrected scores for both HSCT and COWA as the groups were matched for age. When the overall MANOVA indicated an effect of group, this was followed-up by pairwise *t* tests with Bonferroni correction. Effect sizes for all neuropsychological measures comparing BD-R and SZ-R to HC were calculated as Cohen's *d* [8]. In each diagnostic group, linear regression analysis was used to examine whether HSCT category A errors were predicted by the total words generated and total errors made in the COWA. Finally, Pearson's correlations were used to examine the relationship between response time in HSCT inhibition condition and number of errors for the evidence of the trade-off between reaction time and accuracy in each group.

Results

Demographic information and psychopathology ratings for relatives (SZ-R and BD-R) and controls are shown in Table 1. There were no group differences in age ($P = 0.21$), sex ($P = 0.97$), educational level ($P = 0.75$) and full-scale IQ ($P = 0.33$). The three groups differed in terms of total HDRS, YMRS and BPRS (all $P < 0.0001$); this effect was driven primarily by the SZ-R who were statistically more symptomatic than HC on all scales. The BPRS score were highly correlated with those of the other two scales ($r > 0.65$, $P < 0.0001$) and was chosen as a covariate in all analyses as it is more suitable for non-clinical populations.

Details of neuropsychological performance and effect sizes are shown in Table 2 and Fig. 1, respectively. In the HSCT, there was a significant effect of group ($F = 4.429$, $df = 8, 92$, $P < 0.0001$) and FSIQ ($F = 3.260$, $df = 4, 46$, $P = 0.02$) but not symptoms ($F = 0.254$, $df = 4, 46$, $P = 0.90$). Post hoc pairwise comparison showed that SZ-R underperformed compared to HC on all outcome measures (all $P < 0.03$). In contrast, BD-R performed similarly

Table 1 Clinical and demographic characteristics of the sample

	Relatives of SZ patients ($n = 15$)	Relatives of BD patients ($n = 17$)	Controls ($n = 23$)
Age	45.8 (14.2)	38.7 (13.4)	39.0 (13.4)
Education	3.5 (0.9)	3.6 (0.9)	3.7 (0.9)
Sex (female: male)	11:4	13:4	17:6
Siblings/parents/offspring	5:10:0	6:3:8	–
HDRS	0.8 (0.7)[a]	0.1 (0.3)[a]	0.08 (0.2)[a]
YMRS	0.7 (1.03)[b]	0.4 (0.7)[c]	0.1 (0.3)[c]
BPRS	25.6 (0.8)[d]	24. (1.1)[d]	24.2 (0.4)

Apart from sex data shown are mean (standard deviation); *HDRS* Hamilton Depression Rating Scale, *YMRS* Young Mania Rating Scale, *BPRS* Brief Psychiatric Rating Scale, *SZ* schizophrenia, *BD* Bipolar Disorder

[a] Range = 0–2

[b] Range = 0–3

[c] Range = 0–1

[d] Range = 24–28

Table 2 Neuropsychological performance

	Relatives of SZ patients ($n = 15$)	Relatives of BD patients ($n = 17$)	Controls ($n = 23$)
Hayling sentence completion task			
Type A errors	2.8 (2.5)	1.3 (2.7)	0.1 (0.3)
Type B errors	3.8 (1.9)	3.0 (2.2)	0.8 (1.0)
Total time, initiation condition	13.1 (12.9)	4.6 (9.5)	3.5 (5.8)
Total time, inhibition condition	33.2 (27.0)	19.2 (4.4)	8.6 (8.8)
Controlled oral word association			
Total correct responses	43.2 (10.5)	44.7 (8.6)	58.9 (7.5)
Total errors	2.4 (2.9)	0.8 (1.6)	0.08 (0.2)
Intrusions	0.8 (1.1)	0.1 (0.3)	0.001 (0.001)
Perseverations	1.7 (2.0)	0.6 (1.5)	0.08 (0.02)

Data shown are mean (standard deviation); *SZ* schizophrenia, *BD* bipolar disorder; all data shown are raw scores

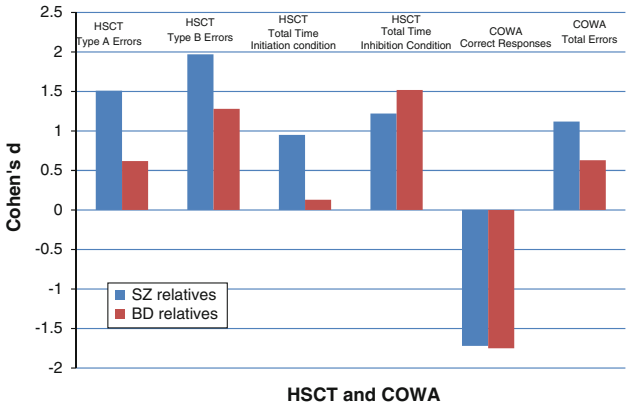

Fig. 1 Cohen's *d* effect size of the difference between controls and relatives of patients with schizophrenia (SZ) or bipolar disorder (BD) in the Hayling sentence completion task (HSCT) and controlled oral word association (COWA)

to HC in all measures ($P > 0.11$), but they committed more type B errors ($P = 0.01$). BD-R performed better than SZ-R in terms of initiation time 1 ($P = 0.007$) and type A errors ($P = 0.03$).

In the COWA, there was a significant effect of group ($F = 9.187$, $df = 4, 96$, $P < 0.0001$) and FSIQ ($F = 3.502$, $df = 2, 48$, $P = 0.03$) but not symptoms ($F = 0.267$, $df = 2, 48$, $P = 0.76$). Both SZ-R and BD-R generated fewer words than HC (all $P < 0.0001$). SZ-R made more errors both compared to HC and BD-R (all $P < 0.03$), whereas there was no statistical difference between the two latter groups (all $P = 0.51$).

In SZ-R (but not in BD-R), linear regression analysis showed that total number of words generated and total number of errors committed in COWA jointly accounted for 42% of variance ($R^2 = 0.50$; adjusted $R^2 = 0.42$; $F(2) = 6.197$, $P = 0.01$) in HSCT category A errors with word generation being the most significant contributor to this association ($\beta = -0.718$, $P = 0.005$).

In SZ-R, HSCT initiation time 2 correlated positively with category A errors ($r = 0.71$, $P = 0.01$), whereas no significant correlations were found for BD-R or HC.

Discussion

In accordance with our hypotheses, we found that relatives of patients with SZ (SZ-R) and relatives of patients with BD (BD-R) had reduced cued word production during the COWA, while error rate was significantly increased in the SZ-R only. In the HSCT, SZ-R showed prolonged response times in the initiation condition and inhibition conditions, while BD-R were slower than controls in the inhibition condition only. Both relatives' groups had a higher error rate than controls but SZ-R made more type A errors. Furthermore, SZ-R but not BD-R, errors in the HSCT were predicted by performance in the COWA. These results were not attributable to general intellectual ability differences between the groups.

With respect to the COWA, relatives' performance mirrors previous results in patients with SZ and BD. Reductions in word production have been found in both SZ and BD patients [4, 16, 29, 33]. Direct comparisons between the two patients' group consistently report that the degree of impairment in word production is greater for SZ than BD patients [16, 20, 32], suggesting that the presence of syndromal SZ has a greater impact than BD in cued word production. The increased error rate in SZ-R compared to controls in this study replicates previous findings [21] and seems to relate predominantly to familial risk for SZ and not BD.

The findings from the HSCT also point to significant difficulties in word production being primarily associated with familial predisposition to SZ given that SZ-R had the longest response time in the initiation condition despite their being given contextually restricted cues. Although

both relatives groups made significantly more errors than controls, SZ-R were more impaired that BD-R and this reached statistical significance for category A errors.

Taken together, these findings suggest that impaired maintenance of contextual information is primarily associated with familial risk for SZ rather than BD. SZ-R experienced delays even when responses were nearly prescriptive. In contrast, the ability to withhold overlearned verbal responses and to switch to task appropriate responses in the inhibition condition of the HSCT emerged as a shared feature of familial risk to both disorders albeit being more pronounced in SZ-R. This pattern may not be unique to language based tests as it has been found in other tasks such as antisaccade tasks [11, 22].

Neuropsychological test performance cannot directly inform about the neural circuitry involved. However, given the wealth of knowledge on the neural correlates of the COWA and HSCT some inferences about the possible brain networks involved is possible. Successful performance during cued word generation relies on the integrated engagement of prefrontal–temporal networks [28]. In these tasks, performance correlates with the degree of activation of the dorsolateral prefrontal cortex (PFC) particularly on the left [28, 38]. The function of the lateral PFC relates to the representation and maintenance of contextual information (in other words "task rules"), which are then implemented in posterior cortical regions. In the case of word production, the most relevant PFC connections are with the lateral superior temporal regions. This is also true of the initiation condition of the HSCT [9]. In contrast, cued word production does not engage the ventral PFC, which only becomes relevant during the inhibition condition [9]. We would therefore suggest that our data point to the primacy of dorsolateral PFC involvement in the pathophysiological mechanisms related to the risk for SZ but not BD. Ventral PFC abnormality, although not unique to BD, may be a core biological correlate for this disorder. This model although appealing and consistent with other work in the field [7, 10, 15, 50] would require further investigation using appropriate neuroimaging techniques.

There are several methodological considerations. The sample size is relatively small, and theoretically it may not be representative of general performance in relatives of people with SZ or BD. This is probably not the case here given the internal consistency of the results, their resonance with existing literature and the magnitude of the observed effect size [5, 40, 44]. Although the relatives included in our study were free of any psychiatric disorder, it is conceivable that they may develop mental health problems at some future point. However, we consider this unlikely since the mean age of both relative groups suggest that most of them were past the risk period for SZ and BD. It is also unlikely that the increased error rate in the HSCT reflects poor motivation or "impulsive" responding. Both relatives' groups significantly increased their response time in the inhibition condition, which is likely to reflect increased effort invested in the task.

Acknowledgments The authors would like to thank Professor Paul W. Burgess at the Institute of Cognitive Neuroscience, University College London, UK for his invaluable help and comments during the study.

Conflict of interest None.

References

1. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington
2. Aron AR (2007) The neural basis of inhibition in cognitive control. The Neuroscientist 13:214–228
3. Arts B, Jabben N, Krabbendam L, van Os J (2007) Meta-analyses of cognitive functioning in euthymic bipolar patients and their first-degree relatives. Psychol Med 9:1–15
4. Balanzá-Martínez V, Tabarés-Seisdedos R, Selva-Vera G, Martínez-Arán A, Torrent C, Salazar-Fraile J, Leal-Cercós C, Vieta E, Gómez-Beneyto M (2005) Persistent cognitive dysfunctions in bipolar I disorder and schizophrenic patients: a 3-year follow-up study. Psychother Psychosom 74:113–119
5. Bora E, Yucel M, Pantelis C (2009) Cognitive endophenotypes of bipolar disorder: a meta-analysis of neuropsychological deficits in euthymic patients and their first-degree relatives. J Affect Disord 113:1–20
6. Burgess PW, Shallice T (1997) The Hayling and Brixton tests. Thames Valley Test Company, Bury St Edmunds
7. Callicott JH, Egan MF, Mattay VS, Bertolino A, Bone AD, Verchinsky B, Weinberger DR (2003) Abnormal fmri response of the dorsolateral prefrontal cortex in cognitively intact siblings of patients with schizophrenia. Am J Psychiatry 160:709–719
8. Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. Lawrence Earlbaum Associates, Hillsdale
9. Collette F, Van der Linden M, Delfiore G, Degueldre C, Luxen A, Salmon E (2001) The functional anatomy of inhibition processes investigated with the Hayling task. Neuroimage 14:258–267
10. Curtis VA, Bullmore ET, Brammer MJ, Wright IC, Williams SC, Morris RG, Sharma TS, Murray RM, McGuire PK (1998) Attenuated frontal activation during a verbal fluency task in patients with schizophrenia. Am J Psychiatry 155:1056–1063
11. Ettinger U, Kumari V, Chitnis XA, Corr PJ, Crawford TJ, Fannon DG, O'ceallaigh S, Sumich AL, Doku VC, Sharma T (2004) Volumetric neural correlates of antisaccade eye movements in first-episode psychosis. Am J Psychiatry 161:1918–1921
12. Ferrier IN, Chowdhury R, Thompson JM, Watson S, Young AH (2004) Neurocognitive function in unaffected first-degree relatives of patients with bipolar disorder: a preliminary report. Bipolar Disord 6:319–322
13. First M, Spitzer R, Gibbon M, Williams J (2002) Structured clinical interview for DSM-IV axis 1 disorders. New York State Psychiatric Institute, Biometrics Research Department, New York
14. Forcada I, Papachristou E, Mur M, Christodoulou T, Jogia J, Reichenberg A, Vieta E, Frangou S (2011). The impact of general intellectual ability and white matter volume on the functional outcome of patients with Bipolar Disorder and their relatives. J Affect Disord. doi:10.1016/j.jad.2010.10.048

15. Frangou S, Haldane M, Roddy D, Kumari V (2005) Evidence for deficit in tasks of ventral, but not dorsal, prefrontal executive function as an endophenotypic marker for bipolar disorder. Biol Psychiatry 58:838–839
16. Frangou S, Dakhil N, Landau S, Kumari V (2006) Fronto-temporal function may distinguish bipolar disorder from schizophrenia. Bipolar Disord 8:47–55
17. Frangou S (2009) Risk and resilience in bipolar disorder: rationale and design of the Vulnerability to Bipolar Disorders Study (VIBES). Biochem Soc Trans 37:1085–1089
18. Golden CJ (1976) Identification of brain disorders by the Stroop Color and Word Test. J Clin Psychol 32:654–658
19. Hamilton M (1960) A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56–62
20. Hawkins KA, Hoffman RE, Quinlan DM, Rakfeldt J, Docherty NM, Sledge WH (1997) Cognition, negative symptoms, and diagnosis: a comparison of schizophrenic, bipolar, and control samples. J Neuropsychiatry Clin Neurosci 9:81–89
21. Hughes C, Kumari V, Das M, Zachariah E, Ettinger U, Sumich A, Sharma T (2005) Cognitive functioning in siblings discordant for schizophrenia. Acta Psychiatr Scand 111:185–192
22. Hutton SB, Ettinger U (2006) The antisaccade task as a research tool in psychopathology: a critical review. Psychophysiology 43:302–313
23. InternationalSchizophrenia Consortium (2009) Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 460:748–752
24. Kempton MJ, Haldane M, Jogia J, Grasby PM, Collier D, Frangou S (2009) Dissociable brain structural changes associated with predisposition, resilience, and disease expression in bipolar disorder. J Neurosci 29:10863–10868
25. Krabbendam L, Arts B, van Os J, Aleman A (2005) Cognitive functioning in patients with schizophrenia and bipolar disorder: a quantitative review. Schizophr Res 80:137–149
26. Kumar CT, Christodoulou T, Vyas NS, Kyriakopoulos M, Corrigall R, Reichenberg A, Frangou S (2011) Deficits in visual sustained attention differentiate genetic liability and disease expression for Schizophrenia from bipolar disorder. Schizophr Res 124:152–160
27. Lelli-Chiesa G, Kempton MJ, Jogia J, Tatarelli R, Girardi P, Powell J, Collier DA, Frangou S (2011) The impact of the Val158Met catechol- O-methyltransferase genotype on neural correlates of sad facial affect processing in patients with bipolar disorder and their relatives. Psychol Med 41:779–788
28. Martin A, Wiggs CL, Ungerleider LG, Haxby JV (1996) Neural correlates of category-specific knowledge. Nature 379:649–652
29. Martínez-Arán A, Vieta E, Colom F, Torrent C, Sánchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugué E, Daban C, Salamero M (2004) Cognitive impairment in euthymic bipolar patients: implications for clinical and functional outcome. Bipolar Disord 6:224–232
30. Maxwell ME (1992) Family interview for genetic studies (FIGS): Manual for FIGS, clinical neurogenetics branch, intramural research program. National Institute of Mental Health, Bethesda
31. McIntosh AM, Harrison LK, Forrester K, Lawrie SM, Johnstone EC (2005) Neuropsychological impairments in people with schizophrenia or bipolar disorder and their unaffected relatives. Br J Psychiatry 186:378–385
32. Mojtabai R, Bromet EJ, Harvey EJ, Philip D, Carlson GA, Craig TJ, Fennig S (2000) Neuropsychological differences between first admission schizophrenia and psychotic affective disorders. Am J Psychiatry 157:1453–1460
33. Nehra R, Chakrabarti S, Pradhan BK, Khehra N (2006) Comparison of cognitive functions between first- and multi-episode bipolar affective disorders. J Affect Disord 93:185–192
34. Perrier E, Pompei F, Ruberto G, Vassos E, Collier D, Frangou S. (2011). Initial evidence for the role of CACNA1C on subcortical brain morphology in patients with bipolar disorder. Eur Psychiatry. doi:10.1016/j.eurpsy.2010.10.004
35. Pompei F, Jogia J, Tatarelli R, Girardi P, Rubia K, Kumari V, Frangou S (2011) Familial and disease specific abnormalities in the neural correlates of the stroop task in bipolar disorder. Neuroimage. doi:10.1016/j.neuroimage.2011.02.052
36. Ruberto G, Vassos E, Lewis CM, Tatarelli R, Girardi P, Collier D, Frangou S (2011) The cognitive impact of the ANK3 risk variant for bipolar disorder: initial evidence of selectivity to signal detection during sustained attention. PLoS One 6:16671
37. Quraishi S, Frangou S (2002) Neuropsychology of bipolar disorder: a review. J Affect Disord 72:209–226
38. Ridderinkhof KR, van den Wildenberg WP, Segalowitz SJ, Carter CS (2004) Neurocognitive mechanisms of cognitive control: the role of prefrontal cortex in action selection, response inhibition, performance monitoring, and reward-based learning. Brain Cogn 56:129–140
39. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, Moore PB (2006) A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. J Affect Disord 93:105–115
40. Snitz BE, Macdonald AW III, Carter CS (2006) Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. Schizophr Bull 32:179–194
41. Spreen O, Strauss E (1998) A compendium of neuropsychological tests, 2nd edn. Oxford University Press, New York
42. Stefanopoulou E, Manoharan A, Landau S, Geddes JR, Goodwin G, Frangou S (2009) Cognitive functioning in patients with affective disorders and schizophrenia: a meta-analysis. Int Rev Psychiatry 21:336–356
43. Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–661
44. Szöke A, Schurhoff F, Mathieu F, Meary A, Ionescu S, Leboyer M (2005) Tests of executive functions in first-degree relatives of schizophrenic patients: a meta-analysis. Psychol Med 35:771–782
45. Takahashi T, Walterfang M, Wood SJ, Kempton MJ, Jogia J, Lorenzetti V, Soulsby B, Suzuki M, Velakoulis D, Pantelis C, Frangou S (2010) Pituitary volume in patients with bipolar disorder and their first-degree relatives. J Affect Disord 124:256–261
46. Torres IJ, Boudreau VG, Yatham LN (2007) Neuropsychological functioning in euthymic bipolar disorder: a meta-analysis. Acta Psychiatr Scand Suppl 434:17–26
47. Ventura J, Lukoff D, Nuechterlein KH (1993) Brief psychiatric rating scale expanded version scales, anchor points, and administration manual. Int J Methods Psychiatr Res 3:227–243
48. Walterfang M, Wood AG, Barton S, Velakoulis D, Chen J, Reutens DC, Kempton MJ, Haldane M, Pantelis C, Frangou S (2009) Corpus callosum size and shape alterations in individuals with bipolar disorder and their first-degree relatives. Prog Neuropsychopharmacol Biol Psychiatry 33:1050–1057
49. Wechsler D (1981) Wechsler adult intelligence scale-revised. The Psychological Corporation, New York
50. Whalley HC, Simonotto E, Flett S, Marshall I, Ebmeier KP, Owens DG, Goddard NH, Johnstone EC, Lawrie SM (2004) fMRI correlates of state and trait effects in subjects at genetically enhanced risk of schizophrenia. Brain 127:478–490
51. Young R, Biggs J, Zieglar V, Meyer D (1978) A rating scale for mania: reliability, validity sensitivity. Br J Psychiatry 133:429–435