Does cognitive performance map to categorical diagnoses of schizophrenia, schizoaffective disorder and bipolar disorder? A discriminant functions analysis.

Discriminant clusters for bipolar and psychosis

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Abstract

Objectives: Despite known overlaps in the pattern of cognitive impairments in individuals with bipolar disorder (BD), schizophrenia (SZ) and schizoaffective disorder (SZA), few studies have examined the extent to which cognitive performance validates traditional diagnostic boundaries in these groups.

Method: Individuals with SZ (n=49), schizoaffective disorder (*n*=33) and BD (*n*=35) completed a battery of cognitive tests measuring the domains of processing speed, immediate memory, semantic memory, learning, working memory, executive function and sustained attention.

Results: A discriminant functions analysis revealed a significant function comprising semantic memory, immediate memory and processing speed that maximally separated patients with SZ from those with BD. Initial classification scores on the basis of this function showed modest diagnostic accuracy, owing in part to the misclassification of SZA patients as having SZ. When SZA patients were removed from the model, a second cross-validated classifier yielded slightly improved diagnostic accuracy and a single function solution, of which semantic memory loaded most heavily.

Conclusions: A cluster of non-executive cognitive processes appears to have some validity in mapping onto traditional nosological boundaries. However, since semantic memory performance was the primary driver of the discrimination between BD and SZ, it is possible that performance differences between the disorders in this cognitive domain in particular, index separate underlying aetiologies.

Cognitive impairment is a hallmark symptom of psychotic disorders including schizophrenia (SZ) and schizoaffective disorder (SZA: Green et al., 2004). Accumulating evidence indicates that patients with bipolar disorder (BD) also have significant impairments in cognitive functioning that may be qualitatively, but not always quantitatively comparable to those seen in psychotic illnesses (Bora et al., 2010; Burdick et al., 2011; Burdick et al., 2015; Harvey et al., 2014; Van Rheenen and Rossell, 2014b). Such impairments are known to impact the capacity for social cognition (Brekke et al., 2005; Van Rheenen et al., 2014; Van Rheenen and Rossell, 2013) and have significant implications for long-term functional outcomes in these disorders, independent of clinical symptomatology (Allen et al., 2014; Fervaha et al., 2014; Green et al., 2004; Van Rheenen and Rossell, 2014c). Indeed, cognitive impairments are likely to be core to the psychopathology of psychosis and BD given that they persist even during times of clinical symptom resolution (Bourne et al., 2013).

Although there are exceptions, on the whole patients with BD generally appear to have cognitive performance that is intermediate to that of SZ and controls (Harvey et al., 2014). Preliminary evidence also suggests that the factor structure of cognitive functioning across the clinical disorders presents in a relatively similar manner, with other research showing that patients with both disorders demonstrate the same *pattern* of impairments across a number of lower-order and higher-order cognitive domains (Barch and Sheffield, 2014; Gogos et al., 2010; Krabbendam et al., 2005; Pradhan et al., 2008; Schretlen et al., 2013).

In the context of current evidence, whether the cognitive impairments seen in SZ and BD represent the same underlying dysfunction remains a matter of debate. On the one hand, it is possible that commonly reported *magnitude* differences in performance between the two, indicate differences in disease-specific variables such as those related to neurodevelopment or clinical course. On the other hand, similarities in the qualitative *pattern* of current cognitive function between BD and SZ compared to controls, suggest that such impairments

could represent biologically meaningful shared features that potentially map onto common underlying genetic mechanisms.

So far, studies assessing cognition across these disorders have generally tended to highlight overlaps or differences in SZ and BD on the basis of quantitative neuropsychological test performance. However such comparisons in and of themselves, provide only weak evidence around whether these disorders are neurocognitively distinguishable, since group-wise comparisons of separate cognitive domains do not assess whether differences in performance magnitude actually validate and reflect distinct diagnostic categories. Thus, the boundaries of nosology cannot be explicitly supported or rejected on the basis of statistical comparisons of such tests by themselves, because it is possible that variance could still overlap between groups on the basis of *a combination* of cognitive factors. Indeed, work by Heinrichs and colleagues (2008) shows that statistically significant magnitude differences in neuropsychological performance do not necessarily translate to diagnostic validation in psychosis spectrum disorders.

Given that recent evidence indicates that the assessment of cognitive performance may help to classify psychiatric illnesses into more clinically or biologically meaningful subtypes (Burdick et al., 2014; Geisler et al., 2015; Hallmayer et al., 2005; Heinrichs, 2005; Lewandowski et al., 2014; Weickert et al., 2000), we aimed to assess the extent to which cognitive vulnerabilities in BD and SZ respect nosological boundaries in individuals carrying these diagnoses. Specifically, we aimed to compare well-matched groups of patients with BD and SZ on a battery of cognitive tests that assess domains of known impairment in these disorders using discriminant functions analysis (DFA). Since it is possible that distinguishing neuropsychological factors for BD and SZ could index separate underlying biological substrates, we were primarily interested in assessing whether there were generalised or specific cognitive domains that could discriminate the disorders diagnostically.

A further research aim was to better understand cognitive functioning in patients with SZA, relative to those with SZ and BD. This relates to a tendency for many past studies to group together individuals with SZ and SZA (Green et al., 2004), despite SZA representing a diagnostic category in its own right. Although SZA does share phenotypic similarities with SZ in terms of persistent psychotic features, the disorder also shares similarities with BD in relation to its mood features (American Psychiatric Association, 2013). The grouping of SZ and SZA patients therefore has the potential to distort cognitive findings and may hamper progress toward elucidating if there are discriminating factors between the disorders. Therefore in this study, we included individuals with SZA in the analysis to determine whether cognitive performance could distinguish these patients as being part of a separate, albeit related, group.

Materials and method

A subset of participants was drawn from a database of individuals who had participated in studies examining cognition in severe psychiatric illness (e.g., see Neill and Rossell, 2013; Tan and Rossell, 2014; Van Rheenen and Rossell, 2014a). Each study was approved by relevant Hospital and University review boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before his or her respective studies began.

Participants

A total of 117 individuals with a DSM-IV-TR diagnosis of SZ (n=49), SZA (n=33) or BD I (n=35, history of psychosis n=26) were included in the analysis. All patients entered the their respective studies with a pre-existing diagnosis of BD, SZ or SZA and their psychiatric diagnoses were confirmed by the MINI International Neuropsychiatric Interview (Sheehan et

al., 1998) or the Structured Clinical Interview for DSM-IV(First et al., 1996) depending on the study through which they were originally enrolled. Patients with significant visual or verbal impairments, a known neurological disorder, and/or a history of substance/alcohol abuse or dependence during the previous six months were excluded. Symptomatology was assessed with the Brief Psychiatric Rating Scale (Overall and Gorham, 1962) and the Montgomery Asberg Depression Rating Scale (Montgomery and Asberg, 1979). All participants were fluent in English, were between the ages of 18 and 65 years, and had an estimated pre-morbid IQ as scored by the Wechsler Test of Adult Reading (WTAR: Holdnack, 2001) of > 75. Demographic and clinical characteristics are presented in Table 1.

Measures

1) *Psychomotor and cognitive processing speed* was measured with total scores on the Digit-Symbol Coding, Trail Making Test-A and scores representing response time performance for the word reading and colour naming trials of the DKEFS Colour-Word Interference Task.

2) *Immediate memory* was measured with the first trials of the Brief Visuospatial Memory Test-Revised and the Hopkins Verbal Learning Test-Revised

3) *Semantic memory* was measured with Category Fluency-Animal Naming[a].

4) *Visual and Verbal Learning* was measured with the sum of Trial's 1-3 of the Brief Visuospatial Memory Test-Revised and the Hopkins Verbal Learning Test-Revised

5) *Working memory* was measured with the Letter Number Span and the Wechsler Memory Scale - Spatial Span backwards.

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[a] Although category fluency is sometimes conceptualised as an executive measure, our past work has shown that category fluency deficits in SZ actually reflect a semantic memory problem rather than an executive one Neill, E., Gurvich, C., Rossell, S.L., 2013. Category fluency in schizophrenia research: Is it an executive or semantic measure? Cognitive Neuropsychiatry 19, 81-95.. Our current conceptualisation of category fluency as a non-executive process fits with this work.

6) *Sustained attention/vigilance* was measured with the Continuous Performance Test-Identical Pairs version

7) *Executive Functioning* was measured with the Neuropsychological Assessment Battery (NAB) Mazes (Planning/Problem Solving) and scores representing response time performance for the interference (inhibition) and interference/switching (cognitive flexibility) blocks of the DKEFS Colour-Word Interference Test[b]

Statistical analysis

We calculated T-scores based on the overall sample means and standard deviations across groups for each test and then created composite scores for each domain of cognition. Scores with inconsistent metrics were reversed to ensure that all scores represented the same metric (i.e., higher scores reflected better performance). Demographic and clinical group differences were assessed via one-way between-groups analysis of variance (ANOVA) or Chi-Square tests. Preliminary bivariate correlational analysis was used to examine the association between the clinical/demographic variables and cognitive domain scores in each of the three groups. Using a conservative alpha value set to $p<.01$, we found no significant correlations between the cognitive domain scores and gender, MADRS or BPRS total score in any of the groups separately. However, some cognitive domain scores were associated with age and age of diagnosis in some of the groups and BPRS scores correlated inversely with attention/vigilance and working memory domains when the groups were considered as a whole. As a result, we regressed out the effects of these confounding variables (age, age at onset and BPRS score) on the cognitive domain scores using regression analyses. We then used the standardised residual scores as predictors in the discriminant functions analysis

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[b] The interference score represents response time controlling for word reading and colour naming, whereas the switching represents response time controlling for word reading, colour naming and interference.

(DFA) predicting group membership into the three diagnostic categories[c]. Factor loadings of <.3 were considered uninterpretable and are not reported. A leave one out classification was used to assess the reliability of the original classification model generated by the DFA. This leave-one-out cross-validation works by deleting each case in turn, and reclassifying the remaining observations by means of the classification rule established in the original model. All tests were corrected at a conservative alpha threshold of $p<.01$.

Results

Descriptive statistics.

Table 1 shows the clinical and demographic characteristics of the sample. There were no differences between the groups in terms of age, gender, illness duration, premorbid IQ and depression severity. A greater proportion of SZ and SZA patients were using antipsychotic medications compared to BD patients, whereas a greater proportion of BD patients were using mood stabilisers/anticonvulsants and antidepressants compared to SZA and SZ patients. SZ and SZA groups both demonstrated higher symptom severity scores on the BPRS compared to BD patients.

[INSERT TABLE 1 ABOUT HERE]

Discriminating cognitive predictors of group membership

Table 2 presents each group's T scores for the cognitive tests, prior to covariate correction, whereas Figure 1 presents a graphical representation of group differences on the cognitive domains using the standardised residual scores which control for age, age at diagnosis and BPRS symptom severity score. A DFA using these residual scores as predictors revealed two functions; the first (see Figure 2) was significant ($p<.01$), explained 22% of the

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[c] Given evidence that psychosis history in BD may impact on cognitive performance, we re-ran the DFA excluding the BD I individuals without a history of psychosis. This made no substantial difference to the significance of the discriminant functions and the pattern of structure loadings (although the classification accuracy did drop substantially) and for brevity is not presented.

variance in the model (Canonical correlation =.47) and maximally separated the SZ group from the BD group. The second function explained only 2.19% of the variance in the model (Canonical correlation=.15) and could not significantly discriminate between the groups. Although the combination of functions was significant (Wilks' Lambda = .76, χ^2=29.67, p<.008), the second function by itself was not (Wilks' Lambda = .98, χ^2=2.41, p=.88).

[INSERT TABLE 2 AND FIGURE 1 ABOUT HERE]

The structure matrix canonical loadings of the predictor variables and the two discriminant functions indicated that the first function was very strongly and positively correlated with semantic memory (canonical loading = .96) and modestly correlated with immediate memory (canonical loading = .37) and speed of processing (canonical loading = .35). Thus, individuals with higher scores on these domains were more likely to be classified into the BD group. Although learning was also correlated to the first function its loading fell below the cut-off, indicating that this variable could only explain only a minimal amount of the functions variance. The second, *non-significant* function correlated with executive function (canonical loading = .76) and attention/vigilance (canonical loading = .44), but the variance shared between these domains was non-discriminant across the disorders.

[INSERT FIGURE 2 ABOUT HERE]

Classification results

As can be seen in Table 3, the original classification results generated on the basis of both functions revealed that only 54.7% of original cases were correctly classified. This modest classification accuracy was largely driven by the high proportion of SZA patients being misclassified as being in the SZ or BD group. On the other hand, the classifier was better able to distinguish SZ and BD patients but showed a bias toward the correct

classification of SZ. The leave-one-out cross-validated classification results were less diagnostically accurate (45.3%) than the original classification results, but largely supported the same classification pattern.

[INSERT TABLE 3 ABOUT HERE]

Given that the low overall classification accuracy could be owed largely to the misclassification of the SZA group, we re-ran the discriminant functions analysis comparing only SZ and BD patients. This analysis revealed a significant single factor solution, comprising the same cognitive domains contained in the first function of the previous analysis. This new single factor solution explained slightly more between group variance (27.14%) and yielded greater overall classification accuracy (original 76.2%, leave one out cross-validation 66.7%) than the previous analysis, correctly identifying a higher percentage of SZ patients (original 84%, leave one out cross-validation 80%) than BD patients (original 65.7% and leave one out cross-validation 48.6%).

Exploratory analysis to identify best discriminating predictor

Given that the significant function was most heavily weighted on one predictor – semantic memory, we re-ran the DFA using a stepwise estimation procedure to ascertain if this predictor could adequately classify patients into diagnostic categories by itself. Indeed, the analysis revealed that only this predictor provided a good fit for the data, maximally separating the SZ group from the BD group and explaining 20.7% of the between-groups variance (p<.000). Classification accuracy on the basis of this single predictor was moderately high, with both SZ and BD patients being classified at a rate of more the 70% in the original model and 68.5% in the cross-validated model. However, no patients with SZA were correctly classified on the basis of this model, with misclassification of this group being biased toward SZ over BD.

Discussion

Although cognitive impairment is a prominent feature of mood and psychotic disorders, the extent to which such impairments explicitly map onto distinct diagnostic classifications is not entirely clear. The aim of this study was to elucidate whether cognitive performance ability in SZ, SZA and BD is related to a general psychopathology, or whether there exist cognitive domains that can separate out each mental illness in a nosologically distinctive way.

A discriminant function analysis revealed a single, significant, discriminating latent function that comprised semantic and immediate memory as well as processing speed. This combination of non-executive cognitive processes was able to maximally separate out SZ patients from patients with BD, explaining 22% of the between groups variance (i.e., whether a participant had a diagnosis of SZ or BD). Semantic memory loaded most strongly on this function and explained 92% of its shared discriminating power[d]. A second function comprising executive functioning and sustained attention/vigilance appeared to separate out SZA patients from those with SZ and BD. However, the additional discriminatory variance explained by this function was very small and non-significant, thus the differences between SZA and BD/SZ groups on the basis of this function were negligible.

Although the initial cross-validated classification score showed only modest classification accuracy, this was likely due to the fact that statistical constraints of the discriminant function analysis meant that the classifier included the second non-significant function as a predictor of group membership. Indeed, when the SZA group was removed from the analysis the accuracy of the classifier improved, but remained supportive of the

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[d] Note that this is not referring to unique variance, but rather variance that is shared with other processes loading on the factor

initial DFA findings that a combination of non-executive cognitive functions was the most parsimonious way to separate patients with SZ from those with BD.

The lack of classifier accuracy for SZA is important, since the diagnosis of SZA as a distinct entity remains a contentious issue in psychiatry (Heckers, 2009; Santelmann et al., 2015). Indeed, it has been argued that rather than being a separate disorder, SZA reflects either a) a comorbid syndrome stemming from within SZ or BD themselves, or b) the intersection of a psychiatric continuum representing the milder end of the former disorder and the more extreme end of the latter (Malhi et al., 2008). Previous neuropsychological findings have shown that magnitude differences in performance between SZ and SZA do not provide validation for diagnostic specificity (Heinrichs et al., 2008), which is consistent with our results. Further, our findings also indicate that the misclassified BD patients tended to be categorised as having SZ rather than the arguably intermediate condition of SZA. Thus in combination, these findings certainly appear to support the notion that, at least in neuropsychological terms, SZA does not represent a diagnostic entity in its own right.

The lack of interpretable loadings for working memory alongside the lack of discriminatory diagnostic power for the attention/vigilance and executive domains suggest that these domains represent clear points of overlap between SZ, SZA and BD. This fits with broader evidence indicating a significant cross-over in the magnitude of impairments in higher level executive and working memory processes between these disorders (Ancín et al., 2013; Glahn et al., 2006). They also support recent findings showing that working memory dysfunction in BD and SZ maps onto the same underlying neural networks, albeit in a graded fashion (Brandt et al., 2014; Hamilton et al., 2009). Indeed, executive and working memory tasks are thought to index the structure and function of prefrontal and cingulate neural regions, of which abnormalities are common to a range of psychiatric illnesses (Amit Etkin et

al., 2013). Thus, cognitive interventions targeting these domains may have broad efficacy, extending beyond traditional diagnostic boundaries (Goodkind et al., 2015).

Since executive functioning, working memory and attention are considered inter-related constructs, it is not surprising that the variance explained by all of these domains together, lacked diagnostic specificity (Diamond, 2013). Nonetheless, work from our group and others shows that executive performance impairments in SZ reflect in part, component process impairments (Neill and Rossell, 2013; Savla et al., 2011). Thus, it could be argued that the lack of group discrimination on the basis of these domains seen here, actually reflects the compounding effect of a more extreme combined impairment of the component memory and speed of information processing skills in the SZ group. This is unlikely to be the case however, given that statistical formulation of the second function occurred whilst controlling for the first. Further, lower level processing speed performance was already partialled out of the Colour Word Interference and Switching scores that formed part of the executive domain used here. Taken together, this suggests that the convergence of executive, sustained attention/vigilance and working memory functions between BD and SZ is not likely to represent simple reflections of performance impairments in SZ more globally. In light of this, it is possible then that the underlying mechanisms of these higher-level cognitive domains may best represent shared, 'cross-disorder' psychopathologies.

It should be noted however, that the error variance that remained after accounting for the diagnostically discriminating factor comprising semantic memory, immediate memory and processing speed was quite large. Despite the linear combination of these cognitive domains showing *some* classification accuracy, a substantial number of BD individuals were still misclassified as having SZ. Further, the stepwise DFA results indicated that semantic memory was a major driver of the discrimination of these groups, offering superior classification accuracy for SZ and BD in the model in which it was the only predictor,

compared to when it was coupled with processing speed and immediate memory. In combination, these findings suggest that diagnostic boundaries between SZ and BD in relation to the less heavily weighted discriminating domains of immediate memory and processing speed are likely to be weak. Thus, we speculate that it is likely that there remain a proportion of individuals with these disorders that resemble each other on the discriminating domains found here more closely than others. This is in keeping with an emerging theme in the literature (Burdick et al., 2014; Lewandowski et al., 2014; Woodward and Heckers, 2015).

Two limitations should be considered in interpreting these results. Firstly, given the variability of medications used by the groups in our sample, it was not possible to partial out their effects. It therefore remains possible that differences in the medications used by the different groups may have had diverse influences on neurocognitive functioning in this study. Secondly, in this paper we incorporated only measures of planning/problem solving, inhibition and cognitive flexibility as the executive functioning measure. Although these are commonly used in the BD and SZ literatures on cognition, the concept of executive functioning is actually much broader than this and it is possible that other executive domains may discriminate the disorders more clearly.

Despite these limitations, the current findings of a lack of diagnostic specificity of performance in the cognitive domains of working memory, executive function and attention/vigilance are informative toward indicating some support for a continuum model of neuropsychological impairment in BD, SZA and SZ. On the other hand, a cluster of more basic cognitive processes appears to have some validity in mapping onto traditional nosological boundaries. Since semantic memory performance was the primary driver of this discrimination between BD and SZ, it is possible that performance differences in this domain in particular, index separate underlying aetiologies. Importantly, since the measure used to

assess semantic memory here – Animal Naming, is closely linked to verbal IQ (Ardila et al., 2000; Miller, 1984; Sumiyoshi et al., 2001), this finding suggests the possibility that the biggest difference between these patient groups is in verbal intelligence. Future studies would do well to substitute this semantic fluency test with a formal measure of current verbal IQ to determine the efficacy that it has in discriminating the patient samples.

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Table 1. *Demographic and clinical characteristics of the sample*

	BD			SZA			SZ			Group comparisons			
	n/%	*M*	*SD*	*n/%*	*M*	*SD*	*n/%*	*M*	*SD*	f/χ^2	*df*	*p*	*Post-hoc comparisons*
N	35			33			49						-
Gender (M/F)	12/23			17/16			23/26			2.26	2	.32	-
Age	40.11	13.48		43.03	9.71			42.57	11.26	.65	2,114	.52	
Premorbid IQ (scaled)		109.26	12.15		103.47	11.10		104.92	9.86	2.64	2,113	.08	-
Age at diagnosis (years)		26.43	13.09		24.99	7.58		24.57	8.00	.92	2,114	.67	-
BPRS		22.66	4.37		35.76	10.53		34.25	8.61	27.12	2,113	.01	BD<SZA & BD<SZ
MADRS		10.86	10.97		9.28	8.89		8.90	7.69	.50	2,112	.61	
% on Antipsychotic	46			94			98			43.53	4	.01	BD<SZ & SZA
% typical	6			3			8			-	-	-	-
% atypical	40			85			86						
% on Antidepressant	46			24			14			14.23	4	.01	BD>SZ & SZA
% on Mood stabiliser/anticonvulsant	69			15			8			46.34	4	.01	BD>SZ & SZA
% on Benzodiazepine	17			6			6			6.23	4	.18	

Post-hoc group differences significant at p<.001; BPRS=Brief Psychiatric Rating Scale; MADRS=Montgomery Asberg Depression Rating Scale; premorbid IQ measured using the Wechsler Test of Adult Reading.

Table 2. *T scores for the cognitive domains, prior to covariate correction*

Cognitive Domain	BD		SZA		SZ	
	M	*SD*	*M*	*SD*	*M*	*SD*
Processing speed	53.33	6.80	49.37	6.34	48.10	7.06
Immediate memory	53.77	8.09	49.34	7.80	48.03	8.31
Learning	53.94	7.12	49.27	8.41	48.09	9.39
Semantic memory	57.42	7.54	49.35	7.06	44.88	8.77
Attention/Vigilance	53.08	9.88	50.21	10.03	48.88	8.15
Working memory	51.91	9.06	48.77	5.78	50.04	8.32
Executive function	50.00	6.58	50.52	6.12	49.50	7.26
Processing speed	53.33	6.80	49.37	6.34	48.10	7.06

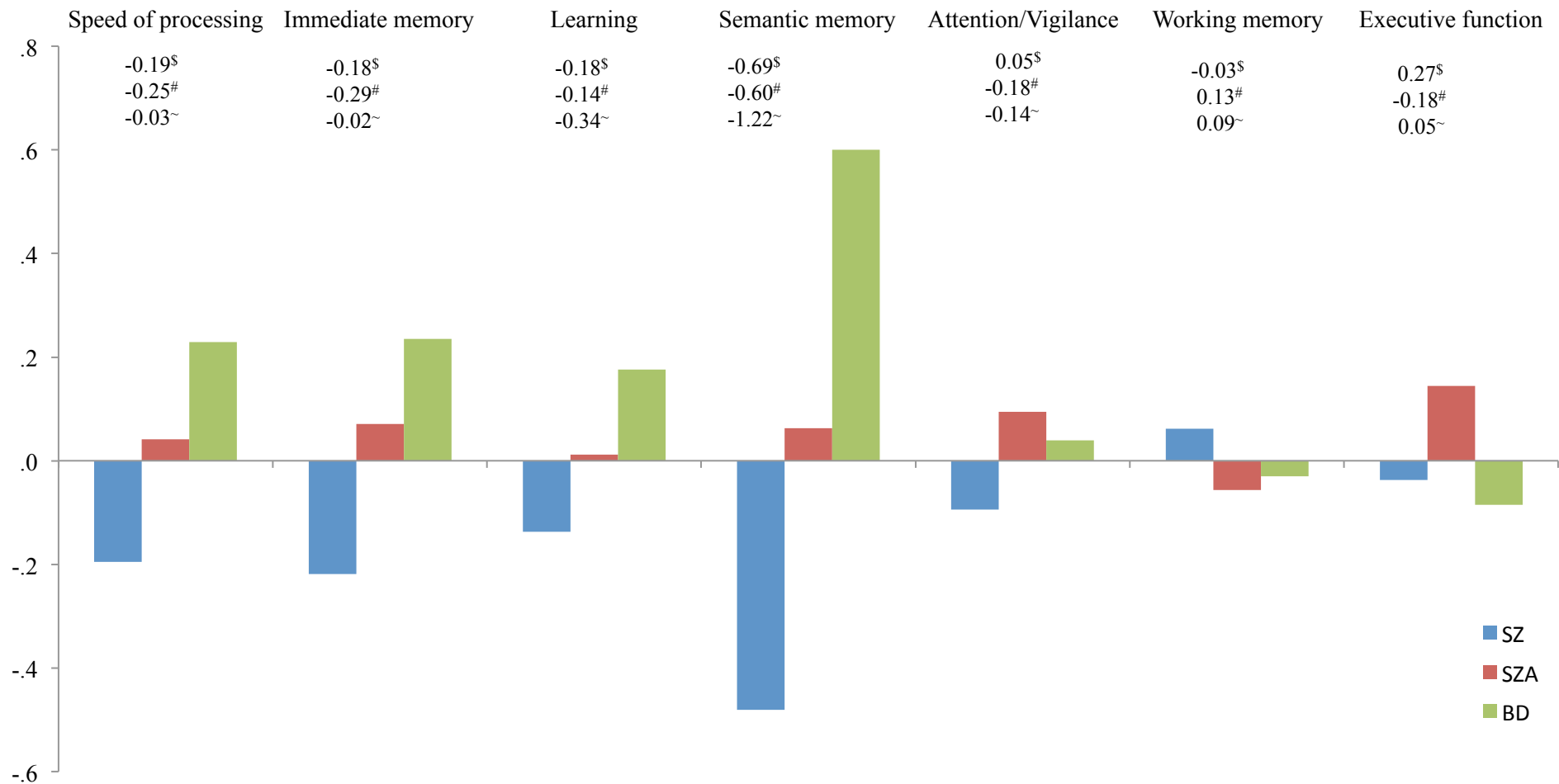Note that the sample mean = 50 and the standard deviation =10

Figure 1. Graphical representation of the residual scores for each of the cognitive domains, controlling for age, BPRS total score and age of illness onset. Note that residual scores are standardised to a mean = 0 and standard deviation =1; $^{\$}$ represents Cohen's d effect size comparing SZA to BD; $^{\#}$ represents Cohen's d effect size comparing SZ SZA; $^{\sim}$ represents Cohen's d effect size comparing SZ BD

Table 3. *Cross-validated classifications*

		Predicted	Membership (%)	
Original		SZ	SZA	BD
	SZ	*73.5*	12.2	14.3
	SZA	42.4	*21.2*	36.4
	BD	34.3	5.7	*60.0*
Cross-validated		SZ	SZA	BD
	SZ	*71.4*	14.3	14.3
	SZA	48.5	*3.0*	48.5
	BD	40.0	11.4	*48.6*

Note that the cross-validation analysis is a means of validating the reliability of the classifier, as each case is deleted in turn from the 'training' sample and is classified by means of the classification rule established on the remaining observations. Italicised values represent % correctly classified.
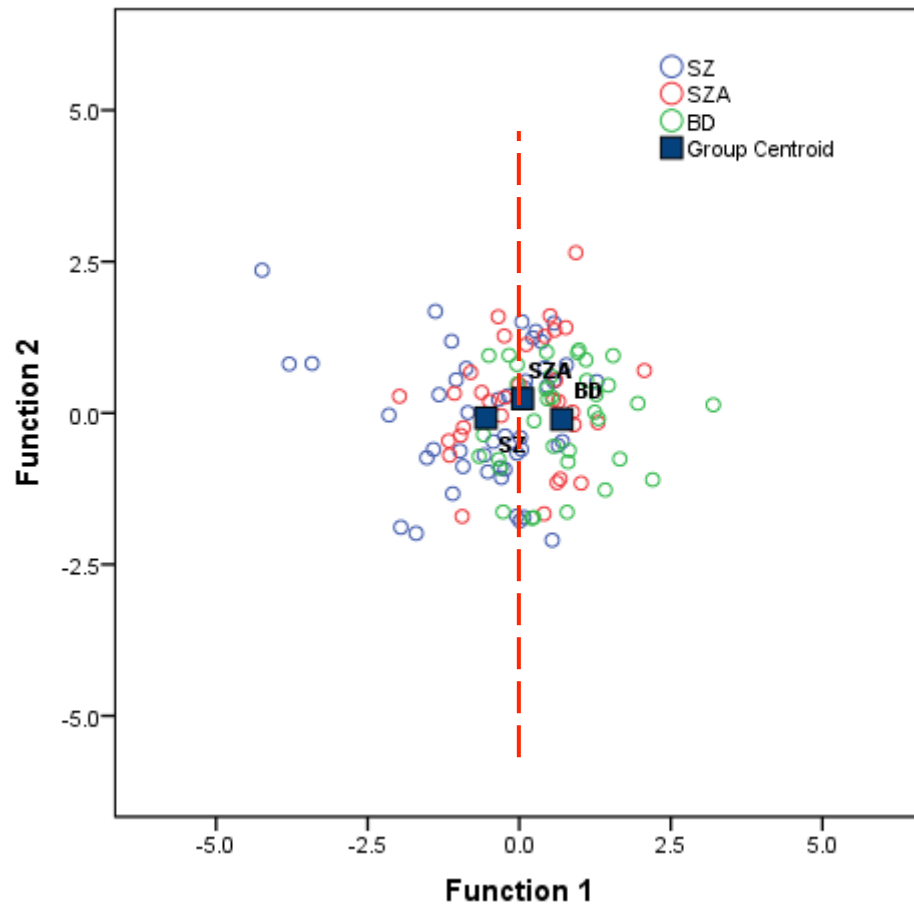
Figure 2. Functions at group centroids; Function 1 maximally separates the SZ group from the BD group (red dotted line). This function remained significant when SZA patients were removed from the model