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Differential semantic processing in patients with schizophrenia versus bipolar disorder: an N400 study

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Short Communication

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Abstract

Objective: Both bipolar disorder (BD) and schizophrenia (SZ) are associated with language and thought symptoms that probably reflect a semantic memory-related impairment. We conducted a preliminary study to explore the nature of semantic processing in these disorders, using event-related potentials (ERPs). *Methods:* Twelve patients with BD, 10 patients with SZ and a matched group of 21 healthy controls (HC) underwent EEG recording while they heard sentences containing homophones or control words and performed a semantic ambiguity resolution task on congruent or incongruent targets. *Results:* Mean N400 amplitude differed between groups for homophones. Patients with SZ made more resolution errors than HC and exhibited a greater N400 congruity effect in ambiguous conditions than BD. In BD, the opposite N400 congruity effect was observed in ambiguous conditions. *Conclusion:* Results indicated differences in semantic processing between BD and SZ. Further studies with larger populations are needed in order to develop neurophysiological markers of these disorders.

Significant Outcomes

- In ambiguous conditions, patients with SZ exhibited a greater N400 difference between congruent and incongruent conditions than patients with BD.
- In ambiguous conditions, patients with SZ exhibited greater N400 amplitude in incongruent conditions than in congruent ones, whereas patients with BD exhibited the opposite N400 congruity effect.
- Ambiguity resolution results suggest that patients with SZ have difficulty considering the context, while patients with BD overactivate the dominant meaning of homophones and have difficulty inhibiting it.

Introduction

Over the past 40 years, both similarities and differences have been identified between the clinical and cognitive symptoms of bipolar disorder (BD) and schizophrenia (SZ). Bleuler's conceptualisation has been reconsidered in clinical terms, opening up new fields of research comparing BD and SZ (Andreasen, 1979). From a cognitive perspective, neuropsychological impairments are core features of both disorders, with no obvious specific neuropsychological signature that can facilitate the diagnostic differentiation between SZ and BD (Bortolato *et al.*, 2015). For instance, patients with BD and patients with SZ both display language and thought symptoms (Andreasen, 1979; Kircher *et al.*, 2014) that are partially subtended by the disruption of semantic processes (Andreou *et al.*, 2013; Jamadar *et al.*, 2013; Piguet *et al.*, 2014), particularly semantic inhibition (Wang *et al.*, 2013; Schneegans *et al.*, 2018). *Semantic inhibition* refers to the inhibition of a primed stimulus that is semantically related to the target (Neumann & DeSchepper, 1991) and occurs only when the semantic network possesses three basic properties: priming, competition and shared activation (Howard *et al.*, 2006). Semantic processes are classically explored in clinical populations with tasks featuring homophones (Brown & Kuperberg, 2015). We can learn more about the time course of these processes and their impairments from event-related potentials (ERPs), especially the N400 component, a negative ERP that is notably modulated by the semantic process of contextual integration (Kutas & Federmeier, 2011). However, only three studies have so far explored the N400 component in BD (Ryu *et al.*, 2012; Cermolacce *et al.*, 2014; Schneegans *et al.*, 2018).

We conducted a preliminary study to look for differences in semantic processing at the electrophysiological level between patients with BD versus SZ. Patients and healthy controls (HC) underwent EEG recording while they performed a semantic ambiguity resolution task featuring

Table 1. Demographic and clinical characteristics of the groups

	Patients ($n = 22$)				
	BD ($n = 12$)	SZ ($n = 10$)	HC ($n = 21$)	F	P
Age	35.92 ± 13.04	43.00 ± 11.47	38.33 ± 10.72	1.05	0.360
Education (years)	13.33 ± 3.14	12.10 ± 2.38	12.24 ± 2.19	0.89	0.419
Verbal IQ	88.92 ± 17.43	81.44 ± 17.56	94.70 ± 12.77	2.37	0.107
BDI	10.92 ± 8.16	10 ± 6.22	4.33 ± 5.52	4.88	0.013 (patients > HC)
YMRS				5.56	0.007 (patients > HC)
TLC				23.91	<0.001 (patients > HC; SZ > BD)
PANSS	–	54.5 ± 13.18	–		
Positive sub-scale	–	11.7 ± 3.16	–		
Negative sub-scale	–	16.1 ± 7.01	–		
General psychopathology sub-scale	–	26.7 ± 5.48	–		
Lithium	25%	–	–		
Antiepileptic	25%	–	–		
Antipsychotics	83%	100%	–		
Antipsychotic mean dosage (mg)	194.33	253.20	–		

IQ, intelligent quotient; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; YMRS, Young Mania Rating Scale; TLC, Thought, Language and Communication scale; PANSS, Positive and Negative Syndrome Scale.

homophones in congruous and incongruous conditions. We predicted that the N400 effect would be modulated differently by semantic ambiguity among patients compared with controls, and among patients with BD versus SZ.

Material and methods

Participants

We included 22 right-handed patients: 12 with BD (4 men) and 10 with SZ (4 men). They all met the relevant *DSM-IV-TR* (American Psychiatric Association, 2000) diagnostic criteria. They were matched for age, education level and verbal IQ (as estimated by Part B of the Mill Hill Vocabulary Scale) with a group of 21 HC (8 men). Participants with intellectual disability, major chronic physical illness, organic mental disorder or substance dependence/abuse (except for nicotine dependence) and uncorrected visual and auditory impairment were excluded. To describe mood symptoms in our populations, we used the Beck Depression Inventory (Beck *et al.*, 1961) and the Young Mania Rating Scale (YMRS; Young *et al.*, 1978) in all groups. Thought and language disorders were assessed with the Thought, Language and Communication scale (TLC; Andreasen, 1979). In the population with schizophrenia, psychopathology was also assessed with the Positive and Negative Syndrome Scale (PANSS; Kay *et al.*, 1986). The demographic and clinical characteristics of the groups are provided in Table 1. No significant difference was found between the two patient groups on antipsychotic dosage ($t = 0.70$, $p = 0.489$).

Ethics statement

This study was conducted at Reims University Hospital, France, between February 2014 and March 2016. It was designed in accordance with the Declaration of Helsinki. The local ethics committee approved the study, and all participants gave their written informed consent before taking part.

Stimuli and design

Participants performed an ERP task of semantic ambiguity resolution adapted from Hoenig and Scheef (2009) and described in Raucher-Chéné *et al.* (2017). Participants heard sentences that ended either with a homophone (ambiguous) or with a control word (unambiguous). Each sentence was followed by a target word displayed on a screen. This target word was either semantically related (congruent) or unrelated (incongruent) to the meaning of the sentence (e.g. featuring the homophone fairy/ferry: 'she looks like a fairy' TALE/BOAT). Participants were asked to decide whether or not the printed target word was related to the meaning of the context sentence they had just heard. The task featured four conditions: congruent ambiguous (CA), incongruent ambiguous (IA), congruent unambiguous (CU) and incongruent unambiguous (IU). Two lists of sentences were randomly used, with 22 or 23 sentences per condition.

EEG recording

Brain activity was recorded during the task via 32 electrodes arranged on the scalp according to the 10-10 system. The reference electrode was positioned at FCz, and the ground electrode was located at AFz. Electrode impedance was held below 5 kΩ. The amplification gain was 1000. To record the electro-oculogram, two electrodes were placed below and on the external canthus of the right eye, and the amplification gain was set at 500.

Preprocessing

The EEG signal was digitised online at a sampling rate of 250 Hz, with bandpass half-amplitude cut-offs of 0.01–100 Hz, and was filtered using a 20-Hz low-pass filter. All the electrodes were re-referenced offline to mean activity at the two mastoids. The EEG was segmented into epochs from 100 ms before target onset to 3000 ms after target onset. Baseline correction was performed for the 100ms period before each target onset. Eye blinks were checked by means of an independent component analysis method.

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Artefacts were also checked by means of an automated analysis performed by BrainVision Analyzer. The following artefact rejection criteria were applied to a period extending 200 ms either side of each epoch: (1) maximum permitted voltage of 50 μV/ms, (2) maximum absolute difference of 100 μV for a 200-ms interval and (3) minimum required activity in a 100-ms interval of 0.5 μV. Only participants with at least 50% (i.e. 11) of usable segments in each condition were retained for the analysis, resulting in the exclusion of two patients with BD and three HC. Thus, 20 patients (10 BD and 10 SZ) and 18 controls were included in the analyses. Artefact-free EEG trials were averaged separately in a 1.7-s time window for each condition: CA (mean number of trials: 19.37 ± 3.11, range: 12–23; HC: 19.89 ± 2.65; BD: 19.60 ± 2.99; SZ: 18.90 ± 3.11); IA (18.76 ± 2.99, 12–23; HC: 20.18 ± 1.70; BD: 18.01 ± 1.94; SZ: 17.9 ± 3.48); CU (19.18 ± 3.11, 12–22; HC: 19.22 ± 2.82; BD: 20.00 ± 2.71; SZ: 18.30 ± 3.09) and IU (19.45 ± 2.41, 12–23; HC: 20.09 ± 2.25; BD: 18.9 ± 2.28; SZ: 19.30 ± 2.17). The mean number of trials averaged in each condition did not differ significantly according to ambiguity, congruity or group, $F(2, 35) = 0.65$, $p = 0.53$. For the ERP data, in accordance with Schneegans *et al.* (2018), we focused our analysis of mean N400 amplitudes on a 400–600 ms time window for three pairs of contralateral centroparietal electrodes (CP1, CP5, C3 on the left hemisphere and CP2, CP6, C4 on the right hemisphere).

Statistical analyses

Statistical analyses were conducted using R software (R Core Team, 2017), as well as the lme4 (Bates *et al.*, 2015), MuMIn (Barton, 2018) and psych (Revelle, 2017) packages and the easieR mega-package (Stefaniak, 2018).

We separately submitted the mean reaction times (RTs), mean percentages of accurate answers and ERP data to a generalised linear mixed model, using an ascending method. Thus, for each analysis, the null model (M0RT/M0AC/M0ERP), including participants as random terms, as well as the intercept parameter, served as the point of comparison for the fit statistics set out in Table 2. We then introduced the effect of each variable of interest in turn to each previous model: (1) ambiguity (homophone vs. control) factor (MaRT/MaAC/MaERP), (2) congruity (congruent vs. incongruent) factor (McRT/McAC/McERP), (3) Ambiguity × Congruity interaction (MacRT/MacAC/MacERP), (4) group (BD vs. SZ vs. HC) factor (MgRT/MgAC/MgERP), (5) Ambiguity × Group interaction (MagRT/MagAC/MagERP), (6) Congruity × Group interaction (McgRT/McgAC/McgERP) and (7) Ambiguity × Congruity × Group interaction (McompRT/McompAC/McompERP). We ran two a priori contrasts to specify the effect of group. The first contrast compared patients (BD and SZ) with HC, and the second contrast compared BD with SZ. To go one step further, we ran Holm-corrected pairwise comparisons between groups on the ERP and accuracy data for the IA condition only, using the phia package (De Rosario-Martinez, 2015).

To test the impact of mood, thought and language disorders or SZ symptoms in our patient populations, we calculated Spearman's correlation coefficients between the clinical data (YMRS, PANSS and TLC scores) and N400 amplitudes recorded on the selected electrodes in the IA condition.

Results

Behavioural results

Mean RT (see Fig. 1(A)) analyses showed a significant effect of congruity, with longer RTs in incongruent conditions (1291 ms) than in congruent ones (1077 ms). The effect of group was also significant, with longer RTs for patients (BD: 1289 ms; SZ: 1285 ms) than for HC (1063 ms), $t(37) = -2.63$, $p = 0.012$, but no significant difference between BD and SZ, $t < 1$.

For accuracy (see Fig. 1(B)), we found main effects of ambiguity, with fewer accurate answers in ambiguous conditions (87.39%) than in unambiguous ones (91.95%), and congruity, with fewer accurate answers in incongruent conditions (86.73%) than in congruent ones (92.6%1). There was also a significant Ambiguity × Congruity interaction, with a greater effect of congruity for homophones (10.21; congruent: 92.49%; incongruent: 82.28%) than for control words (1.56; congruent: 92.73%; incongruent: 91.17%). The main effect of the group was also significant, with fewer accurate responses for patients (BD: 88.67%; SZ: 84.33%) than for HC (93.4%), $t(37) = 3.55$, $p = 0.001$, but no significant difference between BD and SZ, $t(37) = 1.65$, $p = 0.108$. There was a significant Ambiguity × group interaction, as the difference between the unambiguous and ambiguous conditions was greater for patients with SZ (10; control words: 89.33%; homophones: 79.33%) than for patients with BD (1.78; control words: 89.56; homophones: 87.78%), $t(37) = -2.47$, $p = 0.018$, although there was no significant difference between HC (3; control words: 94.9%; homophones: 91.9%) and patients, $t(37) = -1.17$, $p = 0.248$. The Congruity × Group interaction was also significant, as the difference between congruent and incongruent conditions was greater for patients (BD: 8; congruent: 92.67%; incongruent: 84.67%; SZ: 11.78; congruent: 90.22%; incongruent: 78.44%) than for HC (1.18; congruent: 93.99%; incongruent: 92.81%), $t(37) = 3.81$, $p < 0.001$, although there was no significant difference between patients with BD versus SZ, $t(37) = 1.22$, $p = 0.231$. Moreover, there was a significant Ambiguity × Congruity × Group interaction: the effect of congruity was greater for homophones than for control words, and this difference was greater for patients with SZ (homophones: 21.09; congruent: 89.78%; incongruent: 68.69%; control words: 2.67; congruent: 90.67%; incongruent: 88.00%) than for patients with BD (homophones: 9.33; congruent: 92.44%; incongruent: 83.11%; control words: 6.67; congruent: 92.89%; incongruent: 86.22%), $t(37) = -2.73$, $p = 0.009$, whereas the Ambiguity × Congruity interaction did not differ significantly between HC and patients, $t < 1$.

Moreover, when we specifically considered the IA condition, in order to explore the semantic inhibition process, pairwise comparisons revealed fewer accurate answers for SZ (68.89%) than for either HC (89.67%), $\chi^2(1) = 10.80$, $p = 0.001$, or BD (83.11%), $\chi^2(1) = 13.33$, $p < 0.001$, and no significant difference between HC and BD, $\chi^2 < 1$.

ERP results

Analyses revealed a main effect of congruity on ERP data (see Fig. 1(C)), with a greater mean N400 amplitude for incongruent targets (1.78 μV) than for congruent ones (2.45 μV). There was also a significant Ambiguity × Congruence interaction, as the congruity effect was smaller for homophones (−0.31 μV; incongruent: 1.97 μV; congruent: 2.28 μV) than for control words (−1.04 μV; incongruent: 1.59 μV; congruent: 2.63 μV). Finally, the Ambiguity × Congruity × Group interaction was significant. The Ambiguity × Congruity interaction effect varied between BD and SZ, $t(798) = 2.98$, $p = 0.053$, but not between patients and HC, $t < 1$. For patients with SZ, the effect of congruity was greater for homophones (−1.42 μV; incongruent: 2.08 μV; congruent: 3.50 μV) than for control words (−1.00 μV; incongruent: 1.94 μV; congruent:

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Table 2. Fit statistics of the generalised linear mixed models on RTs, mean percentage of accurate answers and mean N400 amplitude

	AIC	BIC	LL	χ^2 (df)	*p*-value	R^2
RTs						
M0RT	2025	2043	−1007			
MaRT	2026	2047	−1006	1.88 (1)	0.171	0.002
McRT	1988	2012	−986	39.16*** (1)	<0.001	0.112
MacRT	1990	2017	−986	0.38 (1)	0.540	0.113
MgRT	1988	2021	−983	6.33* (2)	0.042	0.233
MagRT	1988	2027	−981	3.29 (2)	0.193	0.236
McgRT	1988	2033	−979	3.93 (2)	0.140	0.242
McompRT	1992	2043	−979	0.19 (2)	0.911	0.242
Percentage of accurate answers						
M0AC	1121	1139	−554			
MaAC	1113	1134	−549	10.05** (1)	0.002	0.046
McAC	1100	1124	−542	15.07*** (1)	<0.001	0.123
MacAC	1090	1117	−536	11.83*** (1)	<0.001	0.164
MgAC	1081	1114	−530	12.82** (2)	0.002	0.290
MagAC	1078	1117	−526	6.80* (2)	0.033	0.315
McgAC	1069	1114	−519	13.27**	0.001	0.360
McompAC	1065	1116	−516	7.52* (2)	0.023	0.381
Mean N400 amplitude						
M0RT	4271	4300	−2129			
MaRT	4273	4306	−2129	0.01 (1)	0.927	<0.001
McRT	4270	4308	−2127	5.15* (1)	0.023	0.010
MacRT	4266	4309	−2124	6.07* (1)	0.014	0.013
MgRT	4269	4322	−2123	0.86 (2)	0.650	0.024
MagRT	4270	4333	−2122	2.39 (2)	0.302	0.026
McgRT	4273	4345	−2121	1.32 (2)	0.517	0.028
McompRT	4268	4350	−2217	8.93* (2)	0.011	0.032

AIC, Akakie Information Criteria; BIC, Bayesian Information Criteria; LL, log likelihood for the model; χ^2, difference in deviance between the model and the previous one.
Significance: ***<0.001, **<0.01, *<0.05.
Each model was presented on Statistical Section.

2.94 μV). For patients with BD, we found a similar effect of congruity for control words (−1.39 μV; incongruent: 1.47 μV; congruent: 2.86 μV), but the opposite effect for homophones (+0.61 μV; incongruent: 2.68 μV; congruent: 2.07 μV). When we specifically considered the IA condition (see Fig. 1(D)), in order to explore the semantic inhibition process, pairwise comparisons revealed a smaller mean N400 amplitude for BD (2.68 μV) than for HC (1.52 μV), $\chi^2(1) = 4.18$, $p = 0.041$, but no difference between either HC and SZ (2.08 μV), $\chi^2 < 1$, or BD and SZ, $\chi^2(1) = 2.86$, $p = 0.091$.

Correlations between clinical variables and ERP recordings

No significant correlations were found between clinical variables (YMRS, PANSS and TLC score) and N400 amplitude in the IA condition in the patient group (*p*s > 0.091). Nor was any correlation found between N400 amplitude in the IA condition and mean antipsychotic dosage (*p*s > 0.126).

Discussion

As in a previous study (Raucher-Chéné *et al.*, 2017) conducted with the same semantic ambiguity resolution task, we found congruity effects at both the behavioural and electrophysiological levels. However, the specific objective of the present study was to compare semantic processing both between patients with BD or SZ and HCs and between the two patient groups. At the behavioural level, compared with HC, patients exhibited a greater congruity effect for homophones than for control words, whereas no difference was found between the SZ and BD patient groups. At the electrophysiological level, however, results differed between patients with SZ versus BD. For the former, the N400 congruity effect was greater for homophones than for control words, whereas for the latter, it was great for control words than for homophones.

Our behavioural results are in accordance with the literature showing that both patient populations (SZ and BD) have semantic processing impairments (Brown & Kuperberg, 2015; Schneegans *et al.*, 2018). Many studies have demonstrated a semantic bias in

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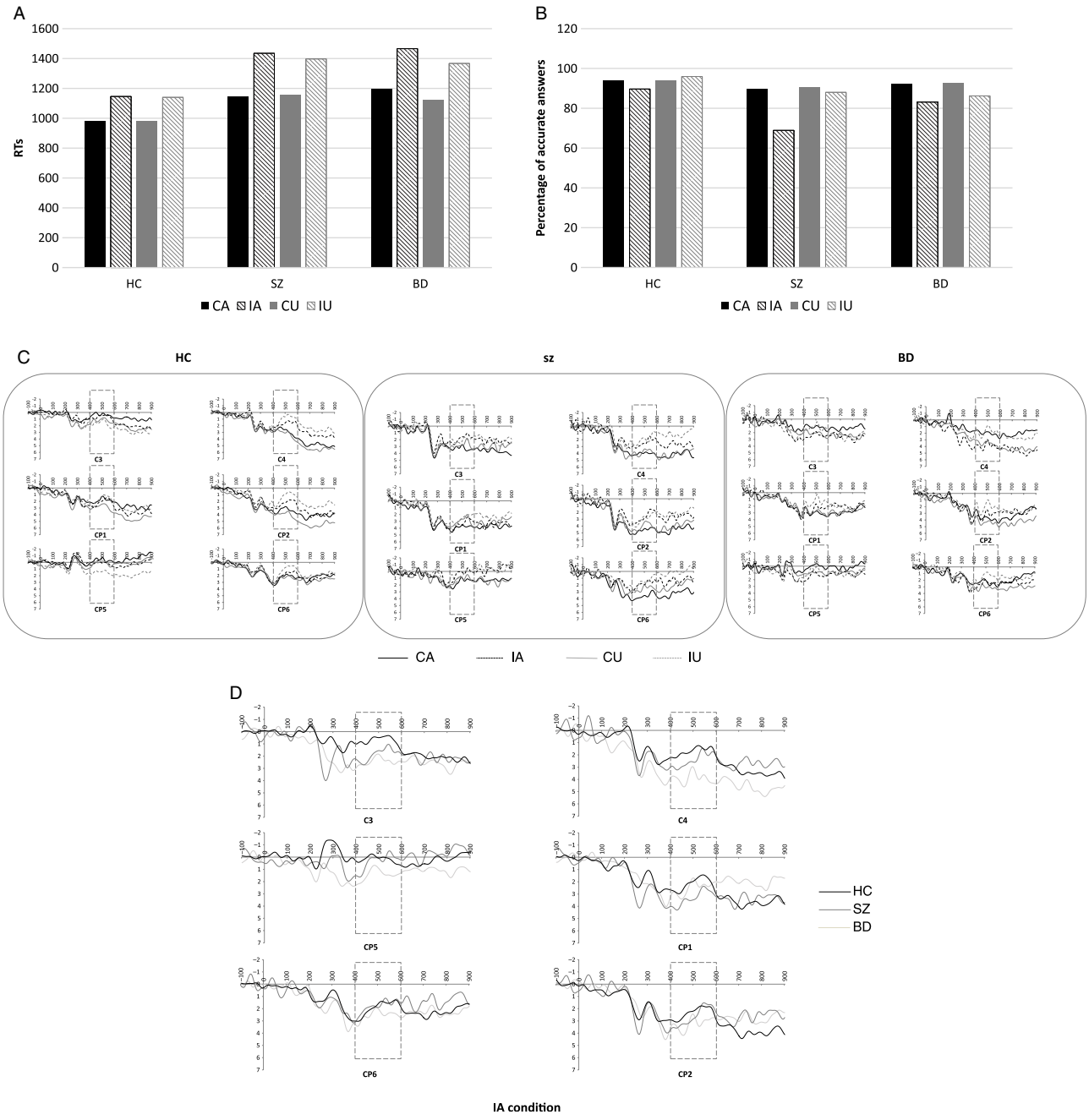

Fig. 1. (A) Mean response times (RTs) in each condition (CA: congruent ambiguous; CU: congruent unambiguous; IA: incongruent ambiguous; IU: incongruent unambiguous) and for each group (HC: healthy controls; SZ: patients with schizophrenia; BD: patients with bipolar disorder). (B) Percentage of accurate answers in each condition (CA, CU, IA, IU) and for each group (HC, SZ, BD). (C) Event-related potentials for the six electrodes in each condition (CA, CU, IA, IU) and for each group (HC, SZ, BD). (D) Event-related potentials in the IA condition for each group (HC, SZ, BD).

interpreting ambiguous words among patients with SZ compared with HC, characterised by difficulty integrating the context (Salisbury, 2010). However, few studies have compared patients with SZ and BD on N400 amplitude. For example, Ryu *et al.* (2012) reported greater N400 amplitudes for congruent words among manic patients and smaller N400 amplitudes for incongruent words among patients with SZ than in other groups.

To take our analyses one step further, we specifically focused on the IA condition eliciting semantic inhibition. No difference was found at the behavioural level between BD and HC, but the ERP results did differ, with a smaller N400 amplitude in patients with BD than in HC. It should be noted that a previous study of hypomanic personality traits found that the higher the Social Vitality sub-score, the smaller the N400 amplitude over the frontocentral region of interest in the IA condition (Raucher-Chéné *et al.*, 2017). Here, we can hypothesise that in patients with BD, the semantic processing impairment stems from overactivation of the dominant meaning of the homophone and difficulty inhibiting this meaning that is perceptible in the N400 modulation, but compensated for at the behavioural level.

Our study had several limitations that need to be addressed, such as the small number of participants, the low number of trials, the putative impact of psychotropic drugs on the EEG waveforms and limitations arising from the material itself, which prevented

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us from exploring the topographical aspects of our results. Nevertheless, the results of our preliminary study exploring semantic processes in patients with BD and SZ support the differentiation of processing between these two populations. Further studies with larger populations are required to understand the mechanisms behind formal thought disorders more clearly and to promote the development of neurophysiological markers that discriminate between these two disorders.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/neu.2019.9.

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Authors contributions. DRC, ST, FG, AK and CBR participated in the conception and design of the study, DRC and ST conducted the data acquisition and analysis and DRC, ST and PG contributed to the drafting of the first version of the manuscript. All the authors read and approved the final version.

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