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Hemispheric cooperation—A crucial factor in schizophrenia? Neurophysiological evidence

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Previous behavioural studies have demonstrated evidence for impaired interhemispheric cooperation in schizophrenia patients. The present study uses event-related brain potentials (ERPs) and source localisations to investigate the neurophysiological mechanisms underlying hemispheric cooperation. Fourteen schizophrenia patients and 15 healthy controls performed a lexical decision task on words and pseudowords presented tachistoscopically either unilaterally to the right or left visual field or bilaterally, with two identical copies, one in each visual field. Behavioural results confirmed earlier findings that healthy controls exhibit a significant bilateral redundancy gain (BRG) for words, which is absent for pseudowords. Schizophrenia patients failed to show the bilateral redundancy gain for words, consistent with a deficit in interhemispheric information exchange. ERPs revealed a significant increase in amplitude approximately 180 ms after stimulus onset, occurring specifically for words in the bilateral stimulation condition. This neurophysiological correlate of the behavioural BRG was absent in patients. Source localisation using minimum norm estimates demonstrated BRG-related enhanced activity in the left temporal cortex for healthy controls, but not schizophrenia patients. Interestingly, behavioural and ERP data indicated a clear left-hemispheric laterality for word processing in healthy participants as well as in patients. Our findings provide behavioural and neurophysiological evidence for reduced interhemispheric cooperation in schizophrenia which may be due to impaired transfer of information from the right to the left hemisphere.

Keywords: Schizophrenia; Bilateral redundancy gain; Interhemispheric transfer; Hemispheric asymmetry; ERP

Introduction

In search for possible alterations of brain mechanisms underlying the psychopathology of schizophrenia, a range of studies have looked at structural and functional brain correlates of behavioural deficits associated with this disease. From the earliest days of schizophrenia research, language has been a principle domain in which symptoms of the disease have been characterised (Bleuler, 1911; Andreasen, 1979). More recent neuroanatomical and neurofunctional research points towards a critical role of language mechanisms in schizophrenia due to evidence of abnormalities in structural brain asymmetry, in particular in areas involved in language processing including, for example, the planum temporale (Falkai et al., 1995). In spite of the agreement on a significant role of language processing in schizophrenia, the precise nature of the deficit and the causal relationship between schizophrenia symptoms, language characteristics and brain abnormality and even a wider symptomatology still remains unclear. In his theoretical framework, Crow (1997a) discussed a functional link between perisylvian language areas, hemispheric dominance for language and the development of schizophrenia symptoms, or more generally, psychosis.

In a meta-analysis, taking handedness, language laterality and structural–anatomical data into account, Sommer et al. (2001) conclude that overall, there is evidence for reduced cerebral laterality in schizophrenia. However, in contrast to this view, a number of studies of linguistic processes did not reveal any behavioural evidence for alterations in functional asymmetry in this patient population (Colborn and Lishman, 1979; Eaton et al., 1979; Magaro and Chamrad, 1983; Mohr et al., 2000, 2001).

In an attempt to resolve some of these issues, it has been suggested that, rather than a change of laterality, an underlying functional problem in schizophrenia may be a deficit in exchanging information between the two cerebral hemispheres, resulting in impairments in hemispheric interaction and cooperation (David, 1994; Crow, 1997b; Friston, 1996). Several studies report structural–anatomical as well as functional evidence in favour of this idea.

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Structural abnormalities have been found in different sections of the corpus callosum (Bilder et al., 1994; Highley et al., 1999). In a meta-analysis of structural MRI studies, Woodruff et al. (1995) report a significant reduction in overall corpus callosum size in schizophrenia patients compared with healthy controls. Downhill et al. (2000) conducted a structural MRI study and showed that compared to healthy individuals, schizophrenia patients showed a reduction in the size of the anterior (genu) and posterior (splenium) sections of the corpus callosum. However, other studies found an increased rather than decreased callosal size in schizophrenia patients (e.g., Bigelow et al., 1983). Still, the structural findings suggest, but do not prove, functional changes affecting the exchange of information between the two cerebral hemispheres. Therefore, it is now critical to ask whether a deficit in interhemispheric communication is present at the neuronal functional level in higher cognitive tasks, especially in language processing.

Earlier work has investigated interhemispheric information exchange in schizophrenia using a range of behavioural tasks (Beaumont and Dimond, 1973; Dimond et al., 1980). A frequently used technique is the lateralised tachistoscopic presentation of stimuli to the left or right visual hemifield (LVF, RVF), or, bilaterally, with identical copies of the stimulus simultaneously flashed to both visual hemifields (BVF). Due to the complete crossing of the visual pathway, lateralised tachistoscopic presentation in one visual field reaches the opposite hemisphere in the first place. Only in the bilateral condition, both hemispheres receive critical stimulus information directly at the same time. By comparing the performance between bilateral and unilateral conditions, it is possible to obtain a measure of the processing difference between the hemispheres and, critically, for the performance of each hemisphere activated specifically compared with bihemispheric simultaneous activation and processing. As two stimuli always imply more stimulus energy than one, there is a need to separate energy-related effects from those originating from higher levels of cognitive processing. This can be done by comparing stimuli exactly matched for physical and psycholinguistic parameters that nevertheless elicit different cognitive processes. For example, words and pseudowords can be exactly matched, although they give rise to different cognitive and neurobiological processes. Words, for example, activate lexico-semantic memory traces, which may be realised as neuronal circuits distributed over both hemispheres (Pulvermüller, 1999). Pseudowords that are pronounceable but meaningless fail to activate a lexical memory trace and a corresponding interhemispheric neuronal assembly. Putting these predictions to a test using the unilateral/bilateral tachistoscopic stimulation paradigm, Mohr et al. (1994, 1996, 2002) found clear evidence for hemispheric information exchange and facilitation for words or familiar faces, but not for meaningless items.

This *bilateral redundancy gain*, BRG, is a robust effect reflecting interhemispheric cooperation (e.g., for words) but is absent or significantly reduced for pseudowords (Mohr et al., 1994; Marks and Hellige, 1999). Importantly, the bilateral redundancy gain for words was found to be absent in schizophrenia patients (Mohr et al., 2000) which argues for impaired interhemispheric cooperation in schizophrenia at the level of lexico-semantic processing. Similarly, a number of previous studies (Beaumont and Dimond, 1973; David, 1987; Lohr et al., 2006; Phillips et al., 1996) report that schizophrenia patients were impaired when they had to match letters, consonant–vowel–consonant (CVC) syllables, digits, abstract shapes or colours between visual fields and hemispheres, but performed well when matching was restricted to one hemisphere only. These behavioural studies make it evident that interhemispheric transmission or cooperation during cognitive processing is impaired. It is now imperative to investigate the neurophysiological basis and correlates of this behavioural deficit with the goal to develop a neurofunctional account of the deficit.

In order to investigate the brain mechanisms underlying impaired interhemispheric transfer in schizophrenia patients, Endrass et al. (2002) measured the evoked potential interhemispheric transmission time (EP-IHTT) during a lexical decision task in which words and pseudowords were presented to the two hemifields. In accordance with previous studies (e.g. Brown et al., 1994), only for words, healthy controls showed faster IHTT after LVF stimulation (right hemisphere) compared to RVF stimulation (left hemisphere). In contrast, schizophrenia patients did not reveal faster transmission times from the right to the left hemisphere. This might indicate a deficit in transferring lexical information from the right to the left hemisphere via the corpus callosum (Endrass et al., 2002; Barnett and Kirk, 2005).

In the present study, we asked whether interhemispheric summation processes related to the BRG can be directly measured using physiological recordings determining the cortical localisation of these processes and their potential alterations in schizophrenia patients.

On the basis of a neurobiological model of word processing, we expected interhemispheric summation for words, but not pseudowords in healthy individuals, based on the assumption that healthy individuals would have intact lexical memory circuits for words (but not pseudowords), distributed over the entire cortex (Pulvermüller and Mohr, 1996). As interhemispheric information exchange is impaired in schizophrenia patients (e.g., Mohr et al., 2000; Endrass et al., 2002; Lohr et al., 2006), neurophysiological signs of interhemispheric summation are predicted to be absent for both words and pseudowords in this case. The critical prediction tested in this study is that the word-specific BRG and its absence in schizophrenia patients shows up in parallel on cognitive–behavioural and neurophysiological measures. If so, the latter may provide clues about the functional abnormality of schizophrenia patients in interhemispheric language processing.

Materials and methods

Participants

Fifteen healthy controls (7 females; mean age: 24 years; education 12 years) and 14 schizophrenia patients (5 females; mean age: 26 years; education: 11 years) were paid for their study participation. All subjects were native speakers of German and strongly right handed as assessed by a short version of the Edinburgh handedness inventory (Oldfield, 1971). None of the participants in the control group had a history of neurological or psychiatric disorders. Subjects of both groups had normal or corrected to normal vision. One-way analyses of variance (ANOVA) found no significant group differences for the variables age, education, and handedness.

All patients were recruited from the Centre of Psychiatry, Reichenau, and met the DSM-IV (Sass et al., 1996) criteria of paranoid schizophrenia. Patients were hospitalised and received antipsychotic medication with a mean dosage equivalent of 293.0 mg (SD=81.5) chlorpromazine (Jahn and Mussgay, 1989). Six patients received atypical and eight patients typical antipsychotic medication. The mean duration of illness was 38.4 months (SD=45.3). Additional clinical variables were taken including the Brief Psychiatric Rating Scale (BPRS, Lukoff et al., 1986) with a mean score of 45.51

(SD = 6.34). Furthermore, the Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) was carried out and a mean total score of 74.1 (SD = 14.0) was obtained (means for positive symptoms were 17.1 (SD = 6.0), 20.1 (SD = 5.8) for negative symptoms, and 36.7 (SD = 7.4) for general psychopathological symptoms). For the Scale for Assessment of Negative Symptoms (SANS, Andreasen, 1983) a mean score of 62.0 (SD = 22.7) was obtained. All clinical ratings were done by two experienced clinicians who were not otherwise involved in the study. Participants were carefully informed of study details and gave written informed consent prior to testing. This study followed the ethics standards and procedures laid down in the *1964 Declaration of Helsinki*.

Procedure

A lexical decision task was carried out in which participants were instructed to decide whether a visually presented letter string was a meaningful word or a meaningless pseudoword by bimanually pressing two out of four response buttons. This was indicated by both index fingers for word decisions and by both middle fingers for pseudoword decisions. Subjects were instructed to respond as fast and as accurately as possible. During the complete experimental block, subjects were requested to fixate their eyes on a fixation cross in the middle of a computer screen.

Stimuli were presented tachistoscopically for 150 ms either unilaterally to the RVF or to the LVF or simultaneously to both visual fields (BVF). The inter-stimulus interval (ISI) varied between 2.5 and 3.5 s. A 60-trial practice block preceded the experiment. The experiment comprised 240 stimuli (120 words and 120 pseudowords), which were presented in pseudo-randomised order. Each item only occurred once during the experiment. The duration of the experiment was approximately 30 min. These methods are similar to earlier studies documenting the BRG (e.g., Mohr et al., 2000).

Stimuli

Words and pseudowords were presented in black upper-case letters on a grey background to reduce visual afterimages. All stimuli were bisyllabic and were four to eight letters long. Words were German content words with a high frequency of occurrence (100–1000 occurrences per 1 million words, according to Ortmann, 1995). Pseudowords were obtained either by permutation of letters within words or by exchanging letters between word stimuli. Pseudowords were pronounceable and orthographically regular but not homophonous to real words.

Stimuli were presented with the Experimental Runtime System software (BeriSoft Cooperation, Frankfurt, Germany) on a 17-in. monitor of an IBM compatible Pentium PC placed at a distance of 1 m in front of the participants. Stimuli appeared between 1.5° and 4.5° of horizontal visual angle, and subtended 0.6° of vertical visual angle. During the experiment, all participants had their chins in a chin rest with a forehead restraint bar centred relative to the viewing screen. Two keypads each comprising two easily manageable micro switches served for response collection and were positioned on a table in front of the participants.

Data acquisition

Event-related potentials (ERPs) were recorded using 64 channels including two EOG channels below the left and right eye. Equal distance electrode caps were used (EasyCap, Falk Minow Services) with Cz as recording reference (all impedances were kept below 5 kΩ). Data were amplified with a sampling rate of 200 Hz by Neuroscan amplifiers (bandwidth DC-30 Hz) and offline high-pass filtered with 0.1 Hz. Data were recorded continuously and stored for offline analysis. After the experimental session, electrode positions were digitised using a 3D digitiser (Polhemus Inc.) to relate individual recordings to a normalised source space. Artifact correction followed the MSEC method (multiple source of eye correction, Berg and Scherg, 1994). Only artifact-free trials with correct responses performed within 2 s after stimulus onset were analysed. The number of trials included in the data analysis did not differ significantly between groups (68.5 ± 8.6% of trials in schizophrenia patients and 72.9 ± 11.3% of trials in the control group).

ERP analysis

ERP data were averaged separately for each of the six conditions (words, pseudowords presented to the LVF, RVF and BVF) and filtered with a 20-Hz low-pass filter. A baseline correction was performed for each participant and each condition by subtracting the average scalp distribution during a 200-ms epoch prior to stimulus onset. After average referencing the ERPs, variability of the electrode positions was reduced by spline interpolation of the data from individually digitised electrode positions on a standardised electrode montage. Finally, data were normalised for each participant by calculating *z*-values for topographical analysis (McCarthy and Wood, 1985).

In a separate analysis, the *bilateral redundancy gain* was analysed by comparing the bilateral condition (BVF) with the right visual field condition (RVF). In order to localise the BRG temporally and topographically, we performed statistical analyses on event-related potential data and on the minimum norm source localisation.

For analyzing evoked potential data, head positions of electrodes were divided into four electrode arrays within each hemisphere: anterior, anterior-central, posterior-central and posterior. Mean amplitudes for each electrode array were determined for words and pseudowords in the three presentation conditions (LVF, RVF and BVF). Global field power analysis revealed that ERPs peaked around 180 ms in all six conditions and both groups. A time window from 150 to 200 ms after stimulus onset was selected for statistical analysis of the BRG because previous studies indicate effects of lexical processing in this time range (e.g., Pulvermüller, 1999; Sereno et al., 2003). Means were compared by analysis of variance (ANOVA) with the between-subject factors Group (controls vs. schizophrenia patients) and the within-subjects factors Lexicality (words vs. pseudowords), Presentation Mode (BVF vs. RVF), Hemisphere (LH vs. RH) and Gradient (anterior, anterior-central, posterior-central vs. posterior). *p*-Values were corrected by Greenhouse–Geisser procedure (if $df > 1$).

Source analysis (minimum norm localisation analysis)

Minimum norm (MN, L2-Norm) estimates were computed in order to look at the location of the neuronal sources or generators underlying ERPs. This was done separately for conditions and participants according to Hauk et al. (2002). Six sensor arrays were selected, each containing a number of sensors over anterior, medial, and posterior areas of the right and left hemisphere. The same time window from 150 to 200 ms as for ERP analysis was chosen.

Statistical analysis was computed using ANOVAs with the factors Group (controls vs. schizophrenia patients), Lexicality (words vs. pseudowords), Presentation Mode (BVF vs. RVF), Gradient (anterior, medial vs. posterior) and Hemisphere (left vs. right).

The data from the control group formed the basis of an earlier publication (Mohr et al., 2007).

Behavioural data analysis

Behavioural data (accuracy and latency) were analysed by ANOVAs with the factors Lexicality (words vs. pseudowords), Presentation Mode (LVF, RVF vs. BVF), and Group (healthy controls vs. schizophrenia patients). Significant interactions were further analysed by planned comparisons using one-way ANOVAs.

Correlational analysis

In the patient group, Spearman correlations were performed on data from clinical rating scales and behavioural and electrophysiological measures. No significant correlations were found.

Results

Behavioural data: accuracy

A significant Group × Lexicality × Presentation Mode interaction was obtained ($F(2,54) = .87$, $p < .02$) (Fig. 1A). Planned comparisons revealed a *right visual field advantage* (RVFA, left-hemispheric superiority) in both groups for words (controls: $F(1,27) = 5.17$, $p < .04$; patients: $F(1,27) = 30.29$, $p < .001$). For pseudowords, only controls showed a significant right visual advantage ($F(1,27) = 6.78$, $p < .02$).

A *bilateral redundancy gain* (BVF minus RVF) was obtained in healthy controls for words only ($F(1,27) = 78.55$, $p < .001$), but not for pseudowords. In schizophrenia patients, no BRG for words or pseudowords was observed.

In addition, a significant Lexicality × Presentation Mode interaction was found ($F(2,54) = 28.82$, $p < .001$). A significant main effect for Group ($F(1,27) = 12.99$, $p < .002$) indicated a better overall performance in controls (82.6 vs. 74.3% correct). Responses to pseudowords were more accurate than to words (Lexicality: $F(1,27) = 5.84$, $p < .03$; 75.4 vs. 81.5%) indicating a response bias towards pseudoword decisions in case of uncertainty. The main effect for Presentation Mode ($F(2,54) = 37.32$, $p < .001$) revealed highest error rates after LVF stimulation (LVF vs. RVF: $F(1,27) = 34.74$, $p < .001$; LVF vs. BVF: $F(1,27) = 48.92$, $p < .001$). As the triple interaction (Group × Lexicality × Presentation Mode, see above) reached significance, the lower order interactions and main effects should not be interpreted.

Behavioural data: latency

In latency data, the three-way interaction of the factors Lexicality × Presentation Mode × Group was close to significance ($F(2,54) =$

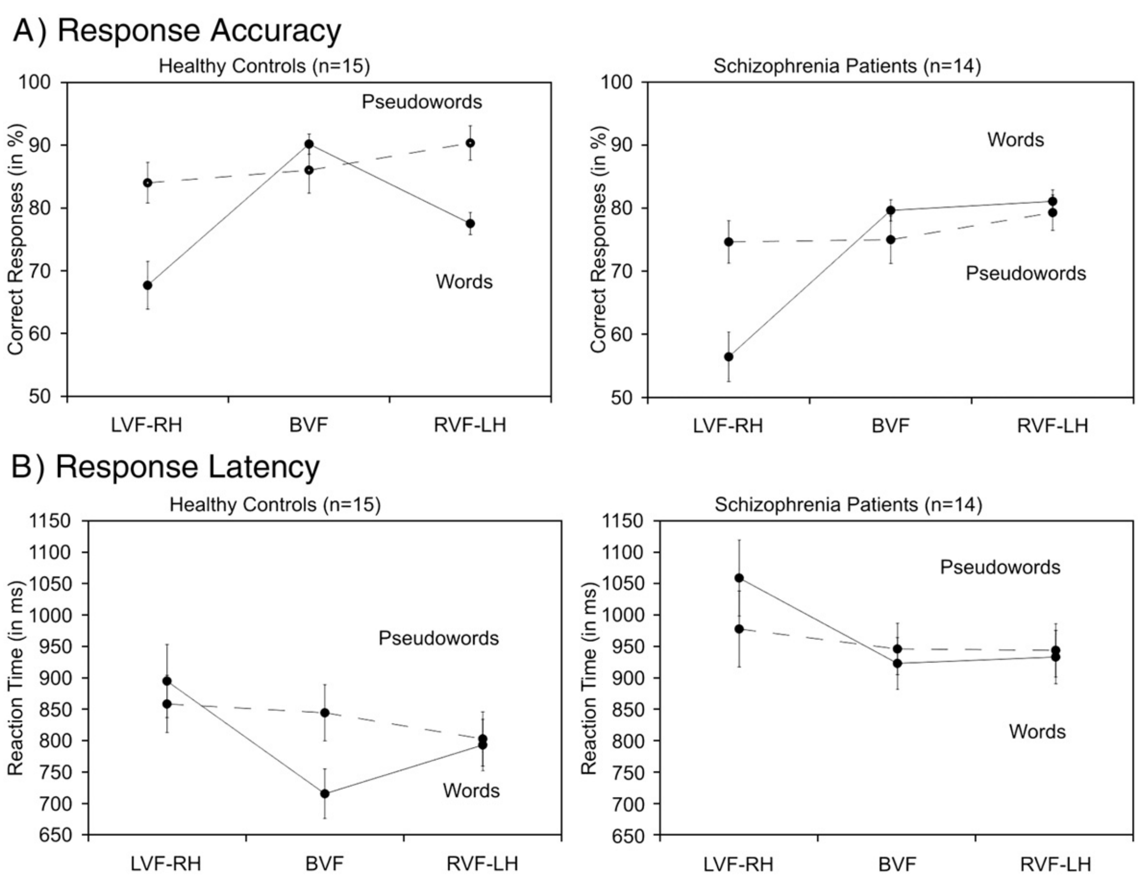

Fig. 1. Behavioural data: mean (standard error in brackets) percentage of correct responses (A) and mean reaction times (B) are displayed for the two groups, presentation conditions, as well as for words and pseudowords. Only healthy controls show a BRG for words.

3.12, $p=.06$) (Fig. 1B). Planned comparisons revealed a *right visual field advantage* for words in both groups (controls: $F(1,27)=8.81$, $p<.007$; patients: $F(1,27)=12.48$, $p<.002$) and for pseudowords only in controls ($F(1,27)=6.91$, $p<.02$). As in accuracy data, a BRG was only observed for words in controls ($F(1,27)=83.41$, $p<.001$). Schizophrenia patients did not reveal a BRG for words, but bilateral performance was superior to LVF performance ($F(1,27)=14.33$, $p<.001$). In addition, there was a significant main effect of Presentation Mode ($F(2,54)=22.18$, $p<.001$) as well as a significant Lexicality × Presentation Mode interaction ($F(2,54)=19.64$, $p<.001$) with a right visual field advantage for words and pseudowords in both groups (words: $F(1,27)=21.18$, $p<.001$; pseudowords: $F(1,27)=8.62$, $p<.007$). Again, the BRG could only be observed for words ($F(1,27)=51.50$, $p<.001$). A significant main effect for group ($F(1,27)=6.16$, $p<.02$) revealed generally faster reaction times in controls than in patients (818 vs. 964 ms).

Event-related potential data

ERP waveforms (Fig. 2) showed a pronounced N100-like component peaking at approximately 180 ms, followed by a long positive deflection (P300-like). There were pronounced N180 differences between bilateral and right visual field conditions which reflect different visual stimulation conditions. In both groups increased N180 amplitudes in BVF compared to RVF presentation were present over the RH.

ANOVAs calculated with ERP amplitudes at parietal electrode sites comparing BVF and RVF condition showed a significant Lexicality × Presentation Mode × Hemisphere × Group interaction ($F(1,27)=4.48$, $p<.05$) (Fig. 2). In order to further examine this interaction separate ANOVAs for left- and right-hemisphere electrodes were computed. Whereas in the RVF condition initial activation was more pronounced in recordings from the contralateral (left) hemisphere, bilateral stimulation should activate both hemispheres simultaneously. Therefore, pronounced differences between BVF and RVF condition were revealed over the right hemisphere with larger amplitudes after bilateral stimulation (Presentation Mode: $F(1,27)=61.61$, $p<.001$). This condition effect was present in both groups but was significantly larger in controls than in schizophrenia patients ($F(1,27)=4.79$, $p<.04$). Analysis of left-hemisphere ERPs (stimulation in both conditions) revealed a Lexicality × Presentation Mode × Group interaction ($F(1,27)=6.44$, $p<.02$). Whereas healthy controls showed a differential effect with enhanced bilateral compared to RVF amplitudes only for words ($p<.05$), schizophrenia patients showed reduced amplitudes after BVF stimulation compared to the RVF condition ($p<.01$) and compared to controls ($p<.05$).

ERP source analysis: minimum norm estimates (MNE)

MNEs from 150 to 200 ms after stimulus onset were calculated. Source topography differences between BVF and RVF conditions are displayed in Fig. 3. Healthy controls showed increased activation

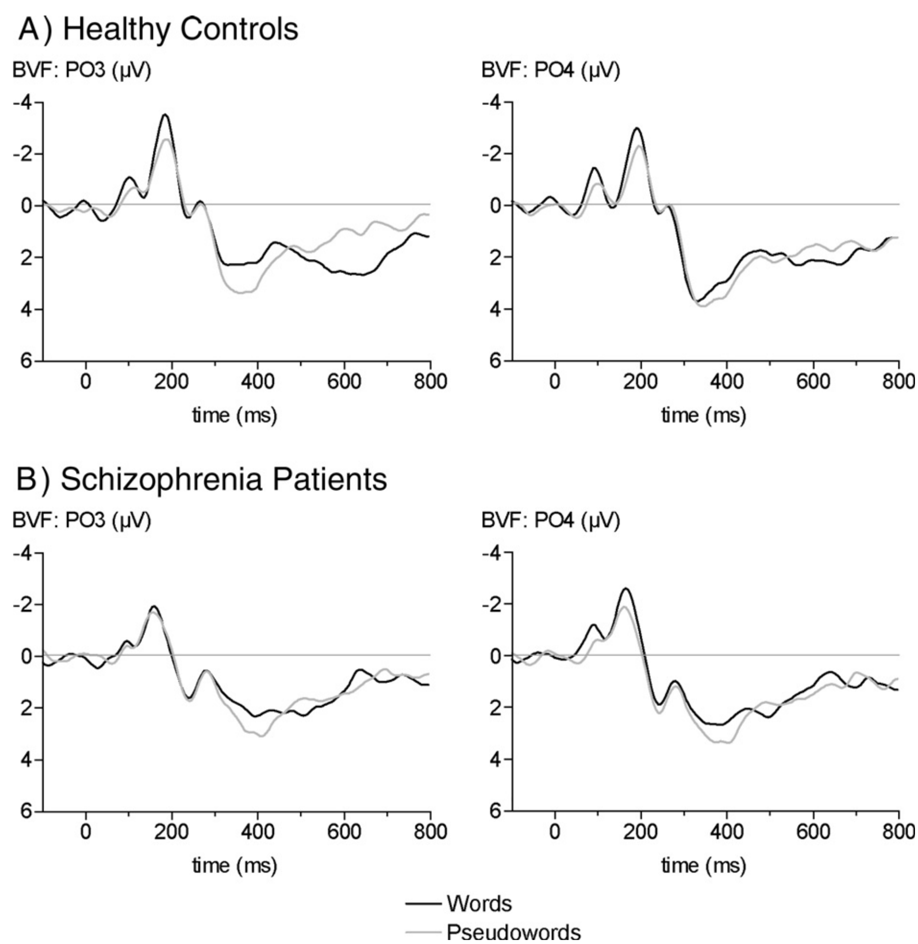

Fig. 2. Grand averages showing ERP waveforms recorded from electrode PO3 and PO4 separately for healthy controls (A) and schizophrenia patients (B) in bilateral (BVF) and right visual field condition. Waveforms elicited by words (black line) and pseudowords (grey line) are superimposed.

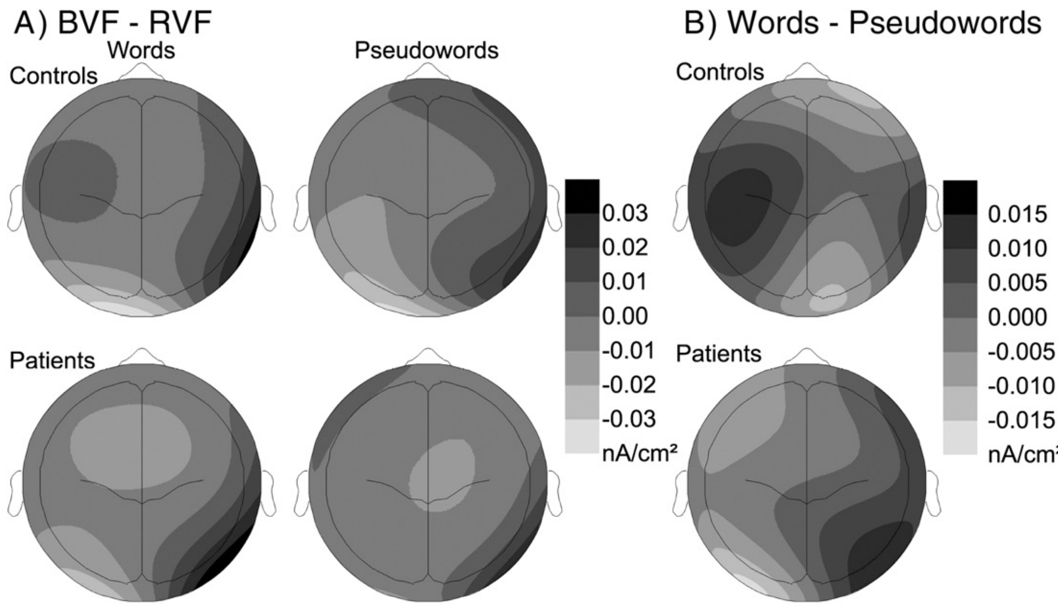

Fig. 3. Brain responses obtained in the time window 150–200 ms after stimulus onset. Source distributions estimated using minimum norm method are displayed. Topographies of source distributions were subtracted between BVF and RVF (A) for words and pseudowords. The double difference (word BVF − words RVF) − (pseudowords BVF − pseudowords RVF) is presented on the right (B). This double difference is the physiological correlate of the BRG. The upper line of maps shows sources in healthy control subjects. The lower line of maps represents sources in schizophrenia patients. Dark areas represent regions of higher electrocortical activity after BVF stimulation and light areas represent higher electrocortical activity after RVF stimulation. A physiological correlate of the BRG was only present in healthy volunteers.

for words in the BVF condition relative to the RVF. This neurophysiological correlate of the behavioural bilateral redundancy gain was present in both hemispheres, but was most pronounced in the left-hemispheric temporal areas (Fig. 3B). In contrast, source estimates for schizophrenia patients suggested an increased activation for words only in the right hemisphere with a more parietal–occipital focus.

In support of a differential BRG in patients and healthy control subjects, a significant Lexicality × Presentation Mode × Hemisphere × Group interaction ($F(1,27) = 7.98$, $p < .01$) was obtained (see also Fig. 3). To further investigate this complex interaction, separate ANOVAs for left- and right-hemispheric recordings were computed. Larger right-hemisphere activation was observed in the bilateral condition compared with the unilateral condition (Presentation Mode: $F(1,27) = 9.83$, $p < .01$). The data revealed a group effect only for left-hemispheric source: Lexicality × Presentation Mode × Group ($F(1,27) = 5.48$, $p < .05$). Enhanced left-hemisphere activation for bilateral compared with right visual field stimulation was found only for healthy controls when words were presented ($p < .05$). This interaction is displayed in Fig. 4.

This enhanced activation for bilateral word processing was not observed in schizophrenia patients. This interaction demonstrates that whereas in schizophrenia patients such activation enhancement was only present in the RH, in controls, a neurophysiological BRG

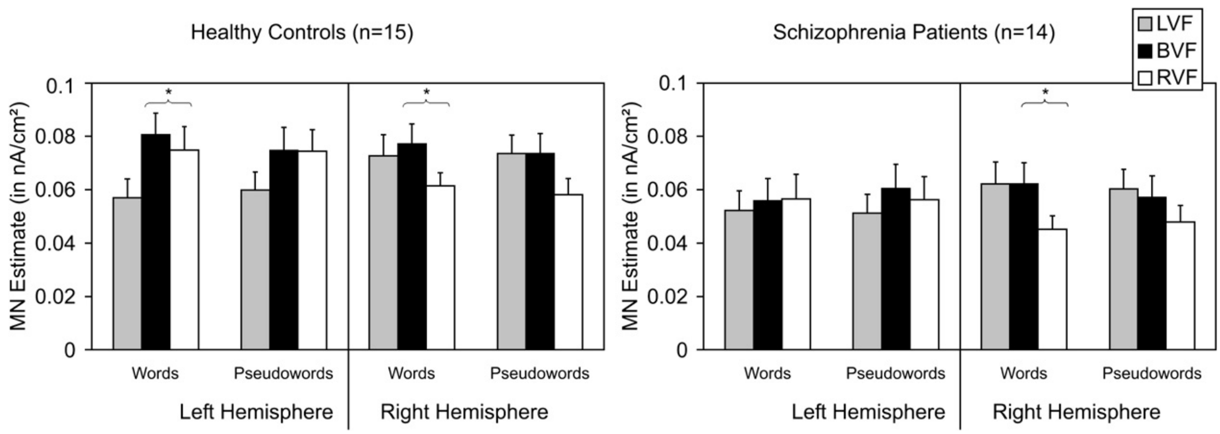

Fig. 4. Source analysis: mean minimum norm estimates in the time range from 150 to 200 ms are reported separately for the two groups, presentation conditions, words and pseudowords, and for each hemisphere. Higher bilateral activation for words was observed in both hemispheres in controls (left picture) and only in the right hemisphere in patients (right picture).

Table 1
Summary of significant main effects and interactions for schizophrenia patients and healthy controls obtained in ERP (I) and MNE (II) analysis is displayed

Factors	F(1,27)	p Value
I. ERPs: comparisons of RVF and BVF conditions		
Presentation Mode × Lexicality × Hemisphere × Group	4.48	<.05
Presentation Mode × Lexicality × Group	6.44	<.02
Presentation Mode	61.61	<.001
Group	4.79	<.04
II. MNEs: comparisons of RVF and BVF conditions		
Group × Hemisphere × Lexicality × Presentation Mode	7.98	<.01
Group × Lexicality × Presentation Mode	5.48	<.05
Presentation Mode	9.83	<.01

was present in both hemispheres. A summary of all significant effects in ERP and MN analyses is displayed in Table 1.

Discussion

In both healthy controls and schizophrenia patients, behavioural data revealed a right visual field advantage for words, consistent with left-hemispheric dominance for the processing of word stimuli presented unilaterally, to the left vs. right visual field. When presentation in both visual hemifields (BVF) was compared to the best unilateral condition (RVF), a word-specific bilateral redundancy gain, BRG, was observed in latencies and accuracies in healthy controls, but not in schizophrenia patients. Importantly, an electrophysiological correlate, an enhanced N180 component, could be shown for this behavioural effect. The word-elicited N180 was enhanced in normal control subjects in the bilateral condition compared with unilateral stimulation, an effect not seen in the pseudoword condition. Schizophrenia patients did not show this neurophysiological correlate of the bilateral redundancy gain.

Behavioural evidence for interhemispheric information transfer in schizophrenia patients

The BRG for words has been discussed as evidence for *interhemispheric cooperation* when processing meaningful information (Mohr et al., 1994; Pulvermüller and Mohr, 1996). Absence of the behavioural BRG in schizophrenia patients may therefore index the impaired transfer of information between the two cerebral hemispheres (for further discussion, see Mohr et al., 2000). The present data now make it possible to relate this behavioural effect to its neurophysiological basis.

Left-hemispheric dominance for processing words (relative to RH processing), as revealed in this experiment, has been reported in numerous studies on lexical processing (e.g., Hellige and Marks, 2001). In the present study, laterality of word processing towards the left hemisphere has been demonstrated by both accuracies and latencies. These results indicate that schizophrenia patients show normal functional laterality at the single-word level. This is consistent with some earlier findings (Magaro and Chamrad, 1983; Mohr et al., 2000, 2001) from behavioural experiments but contrasts with some neuroimaging results (Bilder et al., 1994; Rockstroh et al., 2001) suggesting reduced LH-functional laterality in schizophrenia patients. Differences in stimulus type, task, method and eventually patient selection between studies may account for differences between these findings. We would like to emphasise one particular difference in methods: whereas most previous studies used CVC syllables as stimuli, the present experiment investigated meaningful words. In addition, as opposed to the wider criteria for patient selection in earlier studies, we only tested patients who were strong right handers and excluded ambidexters and left handers, thereby minimizing the effect of handedness on laterality (see also Shapleske et al., 2001).

Neurophysiological correlates of the BRG

As mentioned, behavioural manifestation of the word-specific BRG was observed in healthy control subjects but not in schizophrenia patients. In the same way, the sources of event-related potentials provided an electrophysiological correlate of the BRG in control subjects and absence of this effect in schizophrenia patients. This neurophysiological difference was reflected by the significant Group × Lexicality × Presentation Mode × Hemisphere interaction, revealed by source estimates. Source amplitude differences between words and pseudowords were analysed separately for the left and right hemisphere. In healthy controls, this analysis revealed significantly increased N180 generators bilaterally, which were more pronounced in the left hemisphere for bilaterally presented words (see Fig. 3). Bilateral stimulation with words failed to enhance bihemispheric activation in patients, though. In particular, the strong left-hemispheric source enhancement seen in controls was absent in schizophrenia patients. There was some activity enhancement in the RH which was common to patients and controls (Fig. 2). As left-hemispheric sources apparently failed to receive their activation related to right-hemispheric stimulation with words, these results imply a left-hemispheric processing deficit with implications for language processing.

As stated in the introduction, any electrophysiological correlate of the BRG was expected only for meaningful stimuli as, for example, meaningful words for which memory circuits distributed over both hemispheres have been postulated. A bilateral redundancy gain for these stimuli is a measure of cooperation between the hemispheres and requires intact and efficient interhemispheric transfer of information via the corpus callosum (Mohr et al., 1994). Therefore, it is crucial to note that when looking at ERP amplitudes and minimum norm estimates, pseudoword processing as a control condition differed from word processing and did not give evidence of a physiological BRG or a difference between healthy participants and patients (Fig. 3). The reduced left-hemispheric difference between the source strengths elicited by words and pseudowords seen in patients might therefore be due to inefficient or slowed information transfer within word-related neuronal assemblies comprising far-reaching neurons from different areas of the cortex. This slowed information processing within left temporal–parietal areas might have prevented additional neuronal activation from the RH to reach left-hemispheric circuits in time (cf. Endrass et al., 2002). However, we cannot localise with certainty the deficit in interhemispheric connections. As a further possibility, left-hemispheric circuits receiving direct right-hemispheric input might not be sufficiently effective in integrating activation received from the RH, so that a left-hemispheric deficit could contribute to the absence of the BRG. This interpretation would be in line with the idea that schizophrenia is characterised by a lack of or reduction of left-hemispheric dominance for language (Crow, 1997a,b). Despite the fact that schizophrenia patients clearly show dysfunctions in language such as incoherent speech or neologisms, empirical evidence in terms of abnormal functional lateralisation of language processes or structural laterality (e.g., the planum temporale or sylvian fissure, see Shapleske et al., 2001) is rather inconsistent.

However, it is noteworthy that in the present study, patients did not show direct behavioural evidence for impaired left-hemispheric functions, as evidenced by a normal right visual field advantage, reflecting left-hemispheric superiority for word processing. The functional deficit only affected the redundancy gain for words, but not pseudowords, and it is therefore best explained by a specific functional impairment of word-related transcortical cell assemblies distributed over both hemispheres (see Pulvermüller and Mohr, 1996). As redundancy gains have been observed between and within hemispheres (see, e.g., Mohr et al., 1996), an important next step will now be to find out whether the absence of a redundancy gain in schizophrenia patients will still persist if redundant information is presented within the same hemisphere.

Minimum norm estimates as a measure of source localisation revealed similar results with a significant Group × Lexicality × Presentation Mode × Hemisphere interaction ($p < .01$). Controls, but not patients, demonstrated an increase of activation over both hemispheres (relative to the RVF) when processing words in the bilateral condition (Fig. 3). There was no bihemispheric increase in activation when pseudowords were processed. Overall, minimum norm estimates (source analysis results) suggest that in healthy participants, the BRG for words is associated with an increase in cortical activation in both hemispheres approximately 180 ms after stimulus onset. Therefore, the activation for words in the bilateral condition is not only increased in comparison to pseudowords but also in comparison to words in the RVF condition. Schizophrenia patients did not show these effects. Thus, evidence from MNE measures indicates that schizophrenia patients show impairments in processing meaningful words presented to both hemispheres at the same time. This mirrors the findings in ERP data and offers several possible interpretations. As mentioned earlier, the observed absence of a BRG in schizophrenia patients may be related to a deficit in transferring information from the right hemisphere to the left, leading to decreased interhemispheric interaction or cooperation (Beaumont and Dimond, 1973; David, 1987; Endrass et al., 2002; Lohr et al., 2006; Mohr et al., 2000). Similar impairments of hemispheric transmission in schizophrenia patients were found by Rockstroh et al. (2001). In this study, auditory-evoked magnetic fields were recorded in response to tones and syllables. In schizophrenia patients, only for syllables, the transfer from the RH to the LH (determined from the N180m peak latency) was significantly delayed, whereas the transfer from the LH to the RH was very fast. In controls, no such differences were observed. As dysfunctions of the corpus callosum, such as delayed or incomplete transfer of information from one hemisphere to the other, are only measured indirectly by interhemispheric transfer times, structural abnormalities of that brain area can provide further support for alterations of interhemispheric transfer. Structural deviances of the corpus callosum in schizophrenia have been reported in several studies (Woodruff et al., 1995, 1997; Highley et al., 1999; Downhill et al., 2000).

On the functional level, looking at word processing specifically, Endrass et al. (2001) also reported a delayed electrophysiological response from the right to the left hemisphere in schizophrenia patients (see also Barnett and Kirk, 2005). The observation that interhemispheric transfer is impaired in schizophrenia is consistent with a range of symptoms and features of this disease (e.g., Brown and Jeeves, 1993; Mohr et al., 2000).

In summary, this study revealed a deficit in transferring information from one hemisphere to the other. This was apparent in higher cognitive (language) processing. Impairments in information transfer was equally manifest in behavioural as well as in neurophysiological measures. Neurophysiological data suggest that this processing deficit primarily affects the left hemisphere when processing words presented bilaterally in a redundant fashion. Consistent with early lexico-semantic processing (e.g., Pulvermüller, 1999, 2005), this effect occurred already 200 ms after visual stimulus presentation. Rather than saying that schizophrenia patients lack binding mechanisms between their hemispheres, one may suggest that the cerebral hemispheres in this patient group act more independently of each other than those of healthy individuals (see also Lohr et al., 2006), sharing similar characteristics with split-brain patients for whom a lack of hemispheric cooperation has been reported (Mohr et al., 1994).

In conclusion, the present study provides behavioural and electrophysiological evidence for impaired interhemispheric transmission and cooperation in schizophrenia patients, which might be due to delayed information transfer via the corpus callosum. Future research should now address the question of whether the deficit in redundant processing of linguistic information is specific to interhemispheric interaction or rather a more general characteristic of schizophrenic disorders also affecting processes within one hemisphere.

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