Laterality effects in schizophrenia and bipolar disorder

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Abstract There are numerous reports in the literature of lateralised structural cerebral abnormalities and alterations of the corpus callosum in the major psychoses. In the light of these findings the purpose of this study was to directly compare hemispheric differences and callosal interhemispheric transmission (IT) in schizophrenia and bipolar disorder. To do that we tested schizophrenic (SCZ), bipolar disorder (BD) patients and controls in a simple manual reaction time (RT) task with lateralised visual stimuli (Poffenberger paradigm) which enables one to test both laterality effects and IT time. We found an overall slowing of responses with the right hand in schizophrenics but not in bipolar patients, who, like controls, showed no hand differences. This selective slowing down of the right hand is likely to be related to abnormalities of intrahemispheric cortico-cortical connections in the left hemisphere. In contrast, IT time was similar in SCZ and BD patients and did not differ with respect to controls. Two are the novel findings of the present study: first both SZC and BD share a normal IT of visuomotor information despite the presence of callosal abnormalities. Second, an impairment of intrahemispheric left hemispheric processing is present only in SCZ patients. This represents a potentially important clue to a further understanding of the pathogenetic differences between the two major psychoses.

Keywords Reaction time · Interhemispheric transmission · Hemispheric differences · Major psychoses · Poffenberger paradigm

Introduction

Schizophrenia (SCZ) and bipolar disorder (BD) are major psychiatric disorders of considerable personal and societal cost. Renewed interest in testing the validity of the Kraepelinian dichotomy that distinguishes between SCZ and BD has been motivated by evidence of a considerable degree of overlap in the pathophysiology of the two illnesses (Craddock and Owen 2005; Craddock et al. 2006; Salvatore et al. 2007). As the search for common and unique endophenotypes continues, white matter pathology has emerged as a possible marker of these disorders. Indeed, genes regulating myelin and oligodendrocytes are downregulated in both SCZ and BD (Chambers and Perrone-Bizzozero 2004; Uranova et al. 2004) suggesting oligodendrocyte dysfunction (Davis et al. 2003; Tkachev et al. 2003). In addition, magnetic resonance imaging (MRI) studies have demonstrated impaired intercortical white matter connectivity in both disorders (e.g. Brambilla et al. 2005). These data suggest a possible common physiological mechanism for SCZ and BD specifically involving white matter disconnection ultimately leading to intra- as well as interhemispheric disrupted white matter integrity.
In the last decades it has been recurrently found that hemispheric asymmetries are abnormal in SCZ patients (e.g. see Caligiuri et al. 2005; Bellani et al. 2009) and the overall balance indicates a left hemisphere abnormality (Crow 2008) while in BD the overall picture indicates a right hemisphere malfunctioning (Bearden et al. 2001; Caligiuri et al. 2004) or a diminished hemispheric lateralization (Wilson et al. 2007). As to interhemispheric interactions, recent reviews (Innocenti et al. 2003; Arnone et al. 2008a, b), as well earlier evidence reviewed by Woodruff et al. (1997), reported various abnormalities mostly consisting of a reduced size of the corpus callosum in SCZ and BP patients thus suggesting a reduced interhemispheric cross-talk that has been confirmed by a host of physiological and behavioural studies.

The aim of the present study was to directly compare hemispheric asymmetries and interhemispheric transmission (IT) in SCZ and BD. To do that we used the so called Poffenberger paradigm (PP) devised by Poffenberger (1912) and extensively used to study speed of IT (for reviews see Marzi et al. 1991; Marzi 1999; Zaidel and Iacoboni 2003). It consists of the presentation of brief simple visual stimuli either to the left or the right visual hemifield. The participant is to respond as quickly as possible following stimulus onset with either the hand on the same side as the stimulated hemifield (uncrossed condition) or with the hand on the opposite side (crossed condition). Typically, the averaged two crossed conditions yield a slower reaction time (RT) than the uncrossed conditions and this crossed–uncrossed difference (CUD) is taken as a measure of callosal IT time which in healthy participants (Marzi et al. 1991) is in the range of 3–5 ms but which following callosal resection or congenital absence is considerably increased. In addition to IT abnormalities the PP can give valuable insights on hemispheric differences in basic visual and motor functions by comparing performance in the two visual hemifields and by the two hands independently from IT.

We decided to use the PP because recent functional resonance imaging (fMRI) studies (Tettamanti et al. 2002; Omura et al. 2004; Weber et al. 2005) found a selective activation of the genu of the CC during IT of visuomotor information in the PP paradigm and this CC portion has been reported to be abnormal in SCZ patients by Rotarska-Jagiela et al. (2008) who found with respect to controls a decreased volume of the posterior genu and an abnormal fractional anisotropy (FA) in inferior and superior genu.

Materials and methods

Participants

Forty healthy subjects, 22 medicated patients with a diagnosis of schizophrenia and 16 medicated patients with a diagnosis of BD, took part in the experiment (see Table 1 for clinical and demographic details). All the participants were right-handed, as assessed with the Edinburgh Handedness Inventory (Oldfield 1971). We did not include left-handed individuals in the present study. The patients were recruited from the South-Verona Psychiatric Case Register, a community-based mental health register which refers to the four Psychiatry Services of the city of Verona.

Patients with other Axis I disorders, alcohol or substance abuse, history of traumatic head injury with loss of consciousness, epilepsy or other neurological or medical diseases, including hypertension and diabetes, were excluded from the study. All clinical information was retrieved from psychiatric interviews, the attending psychiatrist, and medical charts (Nosè and Barbui 2008), for clinical details see Table 1.

Since a preliminary analysis did not reveal any reliable difference in the PP between BD I and BD II patients their RT data were merged.

Control individuals had no DSM-IV Axis I disorders, as determined by a brief interview modified from the SCID-IV non-patient version (SCID-NP), no history of psychiatric disorders among first-degree relatives, no history of alcohol or substance abuse, no history of head injury, and no current neurological or medical illness. They were recruited by word of mouth and through advertisements.

All subjects provided signed informed consent, after having understood all issues involved in study participation. The research was approved by the biomedical Ethics Committee of the Verona City Hospital (Azienda Ospedali era di Verona).

Apparatus, stimuli and procedure

The participant was seated with the eyes at 57 cm from the centre of a computer monitor (background luminance 0.001 cd/m²). The presentation of a 2,000 Hz tone of 200 ms duration was the first event on a typical trial. The tone prompted the participant to fixate a small cross in the centre of the screen and to wait for the appearance of a visual stimulus in one or the other hemifield. Fixation duration during stimulus presentation was carefully monitored and the exposure duration of the stimuli was kept brief (96 ms) to prevent stimulus foveation. The tone-stimulus onset interval varied randomly within a temporal window of 800–1,200 ms. The visual stimulus consisted of two horizontally aligned white (luminance = 2.3 cd/m²) squares subtending 1° each which were presented unilaterally and simultaneously at 6° and 8°, respectively, from the fixation point on the horizontal meridian either to the right or left visual hemifield. The use of two stimuli presented unilaterally to one or the other hemifield enabled us to increase speed of stimulus detection.
Participants were to respond as quickly as possible to the appearance of the stimuli by pressing the space bar of a computer with the right or the left index finger in different trial blocks according to an ABBA sequence. The experiment was divided into four sessions (two for each hand) and each session included 2 blocks of 15 left-sided stimuli, 15 right-sided stimuli and 5 catch trials in which only the acoustic tone was presented. RTs faster than 140 ms or slower than 850 ms were considered as anticipations or retards, respectively, and were not included in the statistical analyses. The overall mean of discarded trials was 1.43%. The overall percentage of misses was minuscule (0.58%) and was not further analysed.

Results

A preliminary one-way ANOVA with age as factor revealed a main effect \([F(2,75) = 3.97, P < 0.05]\). Post hoc Bonferroni-corrected independent sample \(T\) tests showed that control subjects were younger than BD \((P < 0.05)\) but not than SCZ patients \((P = 0.37)\) and that there was no reliable difference between SCZ and BD patients \((P = 0.69)\). Therefore, we decided not to include age in the subsequent statistical analyses.

Mean RT for the various hand–hemifield conditions are shown in Table 2.

Reaction time scores were analysed with a mixed two-way ANOVA with visual field (left vs. right) and hand (left vs. right) as within factors and group (controls vs. SCZ vs. BD) as a between factor.

The main effect of group was significant \([F(2,75) = 3.53, P < 0.05]\), post hoc tests showed that SCZ patients (388.59 ms) reacted more slowly \((P < 0.05)\) than healthy controls (342.24 ms). BD patients (378.99) did not significantly differ from either group. The interaction visual field by hand was significant \([F(1,75) = 11.15, P < 0.01]\) and this indicates that the overall population showed a reliable IT time of 4.26 ms which is perfectly within the normal range. The triple interaction visual field by hand by group was far from significance \([F(2,75) = 1.85, P = 0.16]\) with non-reliable group differences in IT time (controls: 7.25 ms; SCZ: 3.95 ms; BD 1.59 ms). Importantly, however, the interaction hand by group was significant \([F(2,75) = 3.06, \ldots]\)

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic and clinical variables for bipolar and schizophrenic patients and normal subjects</th>
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<tbody>
<tr>
<td>Variables</td>
<td>Controls (n = 40)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>39.40 ± 11.74</td>
</tr>
<tr>
<td>Males/females, n</td>
<td>22/18</td>
</tr>
<tr>
<td>Ethnicity (race)</td>
<td>Caucasian</td>
</tr>
<tr>
<td>Age of onset</td>
<td>–</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>–</td>
</tr>
<tr>
<td>Lifetime antipsychotic treatment (years)</td>
<td>–</td>
</tr>
<tr>
<td>PDD/DDD (prescribed daily dose/defined daily dose AP)</td>
<td>–</td>
</tr>
<tr>
<td>PDD/DDD typical AP</td>
<td>–</td>
</tr>
<tr>
<td>PDD/DDD atypical AP</td>
<td>–</td>
</tr>
<tr>
<td>PDD/DDD mood stabilisers</td>
<td>–</td>
</tr>
<tr>
<td>Bipolar type 1/2</td>
<td>–</td>
</tr>
<tr>
<td>Admission rate</td>
<td>–</td>
</tr>
<tr>
<td>BPRS (brief psychiatric rating scale) negative symptoms</td>
<td>–</td>
</tr>
<tr>
<td>BPRS positive symptoms</td>
<td>–</td>
</tr>
<tr>
<td>BPRS mania</td>
<td>–</td>
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<tr>
<td>BPRS anxiety-depression</td>
<td>–</td>
</tr>
<tr>
<td>HDRS (Hamilton depression rating scale)</td>
<td>–</td>
</tr>
<tr>
<td>BRMRS (Bech-Rafaelsen mania rating scale)</td>
<td>–</td>
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</tbody>
</table>

<table>
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<tr>
<th>Table 2</th>
<th>Mean RT in the various hand–hemifield conditions</th>
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</thead>
<tbody>
<tr>
<td>LH–LVF</td>
<td>LH–RVF</td>
</tr>
<tr>
<td>Controls</td>
<td>341.40</td>
</tr>
<tr>
<td>Schizophrenics</td>
<td>380.80</td>
</tr>
<tr>
<td>Bipolars</td>
<td>380.90</td>
</tr>
<tr>
<td>Mean</td>
<td>367.70</td>
</tr>
</tbody>
</table>
SCZ patients (Florio et al. 2002) we found no reliable
patients. A PP performed during ERP recording in control and SCZ
important to test the electrophysiological correlates of IT in
In addition, and perhaps more importantly, it would be
much higher number of patients than in the present study.
is in principle possible that the PP is not enough sensitive to
detect subtle IT anomalies and it might be useful to test a
hand in schizophrenic patients

\[ P = 0.05 \]. Post hoc Bonferroni-corrected paired sample \( T \)
tests showed that only in SCZ patients \( t(21) = 2.19, P < 0.05 \) the right hand was significantly slower (395.80 ms) than the left hand (381.38 ms) in RT (controls:
right hand: 340.71; left hand: 343.77. BD: right hand:
376.93; left hand: 381.05; see Fig. 1).
The relatively limited number of patients did not enable
us to statistically assess the effects of duration of illness and
medication on the PP. However, it is worth pointing out
that the above mentioned study of Rotarska-Jagiela et al.
(2008) found no relationship between duration of illness
and performance in the PP. As to medication, further stud-
ies with a larger cohort of patients are needed.

Discussion

In this experiment we compared SCZ, BD and controls for
the presence of hemispheric asymmetries and for speed of
IT. In accord with a previous study in a different cohort of
SCZ patients (Florio et al. 2002) we found no reliable
difference in IT with respect to controls. Thus, despite the
observed abnormalities in the genu of the CC (Rotarska-
Jagiela et al. 2008), i.e. a structure selectively involved in
IT in healthy subjects, our task did not reveal any impair-
ment not only in SCZ but also in BD patients. Of course, it
is in principle possible that the PP is not enough sensitive to
detect subtle IT anomalies and it might be useful to test a
much higher number of patients than in the present study.
In addition, and perhaps more importantly, it would be
important to test the electrophysiological correlates of IT in
a PP performed during ERP recording in control and SCZ
patients.

However, the important finding of the present study is
that SZC, but not BD patients, showed a selective slowing
down of responses to visual stimuli with the right hand sug-
gestig a left hemisphere impairment in a basic visuo-
motoric function. The absence of this effect in BD patients
is important in that shows that the two psychotic conditions
might differ as far as a left hemisphere malfunctioning is
concerned. A main effect of hand was not reported in a
study by Barnett et al. (2005) employing a modified PP and
event-related potential (ERP) recording in SZC patients and
controls. In accord with the present study these authors did
not find group differences in IT but, in contrast to our
results, they did not report any hand effect. One possible
reason for this discrepancy is that their paradigm, in addi-
tion to unilateral presentations, employed intermingled
bilateral double stimuli presentations while our stimuli
were only presented unilaterally. The presence of bilateral
presentations in Barnett et al.’s might have decreased later-
alised effects because of attentional effects emphasising
diffuse attention to the whole visual field; of course, this
possibility should be specifically assessed with further test-
ing.

What might be the cause of the observed slowing down
of the right hand in SCZ patients? In principle, one possi-
bility is that it might be related to a higher proportion of
left- and mixed handedness in schizophrenia (for a review
see Sommer et al. 2001; Dragovic and Hammond 2005;
Dane et al. 2009). However, this explanation cannot apply
to our study because we excluded non-right-handed indi-
viduals in all three groups of participants. At any rate, one
should consider that in a meta-analysis of experiments
employing the PP in healthy participants including 16 stud-
ies and a total of 320 subjects, Marzi et al. (1991) found a
significant right hand advantage in right handers but there
was no corresponding left hand advantage in left handers
who showed no intermanual differences. Therefore, left
handedness does not seem to be responsible of a left hand
advantage in the PP unless there is an interaction between
left handedness and SCZ, a possibility that merits further
testing. Rather, a likely hypothesis is that the slowing down
of responses with the right hand in SCZ patients reflects an
impairment of cortico-cortical intrahemispheric connec-
tions (see Brambilla and Tansella 2007). A reduced connec-
tivity between posterior parietal cortex and ipsilateral
motor cortex has been recently described by Koch et al.
(2008) in SCZ patients using transcranial magnetic stimula-
tion. In addition, another possibility is an abnormality of
pre-motor areas subserving the speeded response required
by our task. For example, Exner et al. (2006) used a serial
RT task to study implicit motor sequence learning. With
respect to control participants, SCZ patients had signifi-
cantly smaller volumes of the left pre-SMA as assessed by
three-dimensional structural MRI and a correspondingly

Fig. 1 Reaction time differences between hands in the three groups
of participants. One can note an overall speed advantage of controls over
the two other groups and a clear-cut advantage of the left over the right
hand in schizophrenic patients.

\[ \text{RT (ms)} \]

- **Left Hand** vs **Right Hand**
  - **Controls**:
    - Right: 340.71 ms
    - Left: 343.77 ms
  - **Schizophrenics**:
    - Right: 376.93 ms
    - Left: 381.05 ms
  - **Bipolars**:
    - Right: 395.80 ms
    - Left: 381.38 ms
worse performance in sequence-specific implicit motor learning. The Exner et al.’s study was carried out on first-episode patients and used a task different from the present experiment and therefore one should be cautious before extrapolating its results to our own patients. However, the presence of an abnormality in cortical pre-motor processing in the left hemisphere is a likely basis for explaining the present results. Moreover, it is important to mention that a recent meta-analytic study (Ellison-Wright and Bullmore 2009) described white matter abnormalities, as found by measuring FA, in the deep white matter of the frontal and temporal left hemisphere in SCZ patients. In this regard, a diffusion tensor imaging (DTI) result particularly relevant to our hypothesis of an impairment of left intrahemispheric connections in SCZ patients is that obtained by Kubicki et al. (2002) who found that while in healthy subjects the left uncinate fasciculus (UF) was greater than the right this was not the case in chronic SCZ patients. This indicates a larger proportion or density of fibres in the left UF than on the right. Given that the UF is the largest bundle of fibres connecting the temporal lobe with left lateral and orbitofrontal regions the left-side impairment of SCZ patients might contribute to the slower intracortical processing found in the present study. Furthermore, very recently, Miyata et al. (2009) provided DTI evidence of white matter abnormalities in left prefrontal and occipital regions of SCZ patients again supporting an intrahemispheric disconnection hypothesis of SCZ. These results certainly reinforce our hypothesis that the right hand slowing of SCZ patients found in the present study might be related to disconnection in the left hemisphere of circuits linking areas subserving detection of visual stimuli and those triggering the motor response. The present finding may represent the consequence on a simple behavioural task of a more widespread disconnection abnormality affecting the left hemisphere of SCZ but not of BD patients. This left hemisphere disconnection might be the cause of higher-order impairments of SCZ patients such as the specific lack of left dominance in a phonological task recently found with ERP recording by Angrilli et al. (2009).

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