Disturbed temporal dynamics of brain synchronization in vision loss

Michał Bola, Carolin Gall and Bernhard A. Sabel
Otto-von-Guericke University of Magdeburg, Medical Faculty, Institute of Medical Psychology, Magdeburg, Germany

Article info
Article history:
Received 27 September 2014
Reviewed 8 December 2014
Revised 17 December 2014
Accepted 24 March 2015
Action editor Jason Barton
Published online 8 April 2015

Keywords:
Vision loss
Blindness
Neural synchronization
Temporal dynamics
Glaucoma

Abstract
Damage along the visual pathway prevents bottom-up visual input from reaching further processing stages and consequently leads to loss of vision. But perception is not a simple bottom-up process — rather it emerges from activity of widespread cortical networks which coordinate visual processing in space and time. Here we set out to study how vision loss affects activity of brain visual networks and how networks’ activity is related to perception. Specifically, we focused on studying temporal patterns of brain activity. To this end, resting-state eyes-closed EEG was recorded from partially blind patients suffering from chronic retina and/or optic-nerve damage (n = 19) and healthy controls (n = 13). Amplitude (power) of oscillatory activity and phase locking value (PLV) were used as measures of local and distant synchronization, respectively. Synchronization time series were created for the low- (7–9 Hz) and high-alpha band (11–13 Hz) and analyzed with three measures of temporal patterns: (i) length of synchronized-/desynchronized-periods, (ii) Higuchi Fractal Dimension (HFD), and (iii) Detrended Fluctuation Analysis (DFA). We revealed that patients exhibit less complex, more random and noise-like temporal dynamics of high-alpha band activity. More random temporal patterns were associated with worse performance in static (r = -.54, p = .017) and kinetic perimetry (r = .47, p = .041). We conclude that disturbed temporal patterns of neural synchronization in vision loss patients indicate disrupted communication within brain visual networks caused by prolonged deafferentation. We propose that because the state of brain networks is essential for normal perception, impaired brain synchronization in patients with vision loss might aggravate vision problems.

1. Introduction
Humans rely on vision more than on any of the other senses. Consequently, blindness can lead to severe decline in quality of life (Gall, Lucklum, Sabel, & Franke, 2009) and is one of the most feared diseases in the elderly. Several diseases damage the retina or optic nerve and result in loss of vision, including glaucoma, age related macular degeneration (AMD), optic

Abbreviations: PLV, Phase Locking Value; HFD, Higuchi Fractal Dimension; DFA, Detrended Fluctuation Analysis.
* Corresponding author. Otto von Guericke University, Institute of Medical Psychology, Leipziger Str. 44, Magdeburg, 39120, Germany.
E-mail address: bernhard.sabel@med.ovgu.de (B.A. Sabel).
http://dx.doi.org/10.1016/j.cortex.2015.03.020
0010-9452/© 2015 Elsevier Ltd. All rights reserved.
neuritis, and diabetic retinopathy. What they have in common is that the loss of vision is rarely complete. Rather, anatomical damage is mostly partial and diffuse, so is the pattern of visual field loss. In the aging society the prevalence of the conditions causing blindness is on the rise. Thus, we urgently need to better understand the mechanisms of acquired blindness to more effectively prevent vision loss and to develop new strategies of vision restoration.

Traditionally, loss of vision after retina or optic-nerve (i.e., pre-chiasmatic) damage is considered to be the direct consequence of the missing bottom-up (retinofugal) input. This is likely due to the retinotopic and hierarchical organization of the early visual system. Obviously, a percept cannot be created without bottom-up input, but it is the activity of brain large-scale functional networks that gives rise to a unified perceptual experience (Hipp, Engel, & Siegel, 2011; review: Siegel, Donner, & Engel, 2012). In contrast to the serial and hierarchical structure of early processing stages (up to V1), processing of visual information in cortical networks is rather distributed, parallel, and recursive (de Haan and Cowey, 2011). Functional networks dynamically integrate information in space and time, which is the basis for binding of different elements of the percept and for coordination of vision with other cognitive functions, such as attention and motor control. Thus, if vision loss affects the state of the large-scale brain network this likely has perceptual and behavioral consequences.

Pre-chiasmatic visual system damage results in anterograde morphological degeneration of the deafferented structures located along the visual pathway, including LGN, optic tract, and V1 (Bogorodzki et al., 2014; Boucard et al., 2009; Frezzotti et al., 2014; review: Gupta & Yücel, 2007; Hernowo, Boucard, Jansonius, Hooymans, & Cornelissen, 2011; Hernowo et al., 2014; Plank et al., 2011). Further, a number of studies found that the deafferented lesion projection zone (LPZ) in V1 can be activated by a stimulus presented in the adjacent intact visual field area, and this was interpreted as a sign of intrinsic V1 reorganization (Baker, Peli, Knouf, & Kanwisher, 2005; Baseler et al., 2011; Dilks, Baker, Peli, & Kanwisher, 2009; Haak et al., 2014; Liu et al., 2010; Schumacher et al., 2008; but see: Smirnakis et al., 2005; review: Wandell & Smirnakis, 2009). Yet, not much is known about the functional state of large-scale brain networks and their possible influence on perception. Apparently, the spread of visually-driven activity is more extensive in patients, as simple visual stimuli, which in normal subjects activate V1 only, in patients activate also the extrastriate visual cortex (Toosy et al., 2002, 2005; Werring et al., 2000). Further, strength of the resting-state fMRI functional connectivity between visual regions changes in optic neuritis (Gallo et al. 2012) and in glaucoma patients (Dai et al. 2013; Song et al. 2014). This includes increased strength of some connections and decreased strength of others. But the clinical relevance of these findings remains vague.

The majority of hitherto conducted studies in patients with vision loss used fMRI to map the spatial pattern of changes in activation or connectivity. Yet, neural activity is organized not only in space but also in time. Perceptual and cognitive operations are rapid and typically comprise several processes executed in parallel which makes temporal coordination essential. Even when no task is carried out, i.e., in the resting state, neural synchronization fluctuates in time and exhibits highly complex temporal patterns (Linkenkaer-Hansen, Nikouline, Palva, & Ilmoniemi, 2001; Stam & de Bruin, 2004). Various pathological conditions were linked to disruption of temporal patterns of brain activity including depression (Linkenkaer-Hansen et al., 2005), Alzheimer’s disease (Montez et al., 2009), schizophrenia (Nikulin, Jönsson, & Brismar, 2012), epilepsy (Monto, Vanhatalo, Holmes, & Palva, 2007), and stroke (Zappasodi et al., 2014). High temporal complexity, in turn, might be identified with a rich repertoire of functional states which support the emergence of perception and behavior (Garrett et al., 2013; Goldberger et al., 2002).

We have recently shown that in patients with vision loss caused by pre-chiasmatic lesions spatial patterns of functional connectivity are impaired (Bola et al., 2014). Specifically, we observed that vision loss was associated with impaired synchronization in the high-alpha band (11–13 Hz). This prompted us to learn more about the temporal aspects of functional activity and connectivity in visual system networks of partially blind patients. Therefore, we studied temporal dynamics of cortical synchronization with the following hypotheses: (i) due to prolonged sensory deprivation the spontaneous activity of the visual network is disturbed and exhibits less complex, more random temporal patterns; and (ii) greater complexity of temporal dynamics is associated with better vision in patients.

2. Materials and methods

2.1. Subjects

The study sample consisted of 19 patients (Table 1) with chronic pre-chiasmatic (i.e., retinal and/or optic-nerve) visual system damage and 13 control subjects that had no neurological dysfunctions. Their data were already analyzed by different methods and published elsewhere (Bola et al., 2014). Patients and control subjects did not differ in age [patients: 53.4 ± 3 yrs, range (20–73); controls: 46 ± 5 yrs, range (20–74); t(30) = 1.28, p = .20]. Inclusion criteria for patient entry into the study were: (i) chronic visual system damage (>6 months of lesion age); (ii) sufficient fixation ability to conduct visual field measurements; and (iii) presence of residual vision detected by perimetry. Four patients had unilateral optic neuropathy (one eye intact) and the others bilateral optic neuropathy. The patients’ diagnoses were taken from their medical records of the referring professionals. Medical records provided information about ophthalmological assessment and, if available, results of structural imaging of the brain.

2.2. Static perimetry, kinetic perimetry, and visual acuity

Visual fields were measured with a Twinfield perimeter (Oculus, Lynnwood, WA) that had a video camera to evaluate eye movements, pupil size and fixation ability. During static 30’ perimetry 66 target stimuli (size: III/4 mm², color: white, luminance: 318 cd/m²/0 db, duration: .2sec) were presented with a fast threshold strategy on a background with constant
luminance of 10 cd/m². To verify proper fixation, four target stimuli were presented inside the blind-spot, and these trials were later excluded from further statistical analysis. Parameters derived from static perimetry were the foveal threshold, the mean threshold averaged across all tested positions excluding the blind spot, the number of absolute (misses of stimuli presented with maximum luminance) and relative defects (stimulus detections at increased luminance above the physiological adequate threshold).

In kinetic perimetry the target (0 dB) was moved from the periphery towards fixation at a constant velocity of 2/C14/sec. The visual field border was then determined for all 24 meridians randomly.

Visual acuity was measured monocularly with and without corrected refraction using a Snellen test chart at a distance of 6 m for distance vision and the Landoldt-ring test at a distance of 40 cm for near vision.

2.3. EEG analysis

2.3.1. EEG acquisition

EEG was recorded with a BrainAmp amplifier (Brain Products, Munich, Germany) using 30 sintered Ag/AgCl electrodes mounted in an elastic cap according to the 10-10 system. Specifically, we used the following electrodes: EOG, Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, TP9, T7, C3, Cz, C4, T8, TP10, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2. For the recording a nose-tip reference was used and a ground electrode was placed between Fz and Cz. The signal was acquired with a 5 kHz sampling frequency, high-pass (.016 Hz) and low-pass (1000 Hz) filtered, and A/D converted (16 bit). Subjects were seated in a dimly lit room and asked to keep eyes closed during the recording.

2.3.2. EEG preprocessing

Analysis of the EEG data was carried out in Matlab and EEGLab (Delorme & Makeig, 2004). The first 60 sec of the EEG signal was used for analysis. The sampling frequency was 500 Hz and the signal was re-referenced to the averaged common reference. Our previous study revealed that high- but not low-alpha band activity is disrupted by vision loss (Bola et al., 2014). Thus, here we focused our analysis on the two alpha sub-bands: low alpha (alpha I; 7-9 Hz), where we expected no differences between patients and controls, and high alpha (alpha II; 11-13 Hz) where between groups differences were expected. Since our focus was on temporal dynamics we aimed to prevent extensive temporal integration caused by filtering. Therefore, the filter order of the band-pass FIR filter was set to two cycles of the lowest cut-off frequency (142 and 90 points for alpha I and alpha II respectively). Hilbert transform (Matlab function hilbert) was applied to band-pass filtered EEG signals to obtain discrete time analytic signals (Fig. 1).

For the present analysis we wanted to obtain continuous EEG signals of the same length from each participant. Therefore, we did not reject noisy parts of the EEG during preprocessing. Yet, it is unlikely that our results are contaminated by artefacts, as firstly, resting-state eyes closed was analyzed which contains less eye- and muscle-related artefacts, and secondly, we analyzed only the alpha band which is typically neither contaminated by low frequency (e.g., eye movements) nor by high frequency artefacts (e.g., miographic activity).

2.3.3. Synchronization measures

Our analysis focused on the temporal dynamics of brain synchronization using two measures: (i) amplitude (power) of alpha-band oscillations and (ii) alpha-band functional

Table 1 – Demographic and clinical characteristic of patient sample. “MD” indicates missing data.

<table>
<thead>
<tr>
<th>ID</th>
<th>Sex</th>
<th>Age [months]</th>
<th>Lesion Etiology</th>
<th>Acuity Near R/L</th>
<th>Far R/L</th>
<th>Static perimetry threshold [db]</th>
<th>Kinetic perimetry [deg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>20</td>
<td>53 Leber hereditary optic neuropathy</td>
<td>.02/.02</td>
<td>0/0</td>
<td>9/0 1.7/.12</td>
<td>36.2/35.5</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>58</td>
<td>8 AION</td>
<td>1.4/1.4</td>
<td>1.2/.24</td>
<td>24/16 1.7/.35</td>
<td>55.8/46</td>
</tr>
<tr>
<td>3</td>
<td>W</td>
<td>24</td>
<td>51 Optic neuritis</td>
<td>1.4/1.4</td>
<td>1.2/.12</td>
<td>30/28 22.3/15</td>
<td>59/69.5</td>
</tr>
<tr>
<td>4</td>
<td>W</td>
<td>68</td>
<td>14 AION</td>
<td>.9/2</td>
<td>.8/8</td>
<td>19/23 5/6</td>
<td>34/38</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>71</td>
<td>113 AION</td>
<td>.5/.13</td>
<td>.4/.17</td>
<td>21/20 10/16</td>
<td>54/58</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>73</td>
<td>170 Non-arteritic ischemic optic neuropathy</td>
<td>.8/.25</td>
<td>1.2/.17</td>
<td>20/14 7/7</td>
<td>48/50</td>
</tr>
<tr>
<td>7</td>
<td>W</td>
<td>49</td>
<td>6 Resected tuberculum sellae meningioma (WHOI)</td>
<td>.9/0</td>
<td>.8/0</td>
<td>22/0 4/.4</td>
<td>13.9/9.4</td>
</tr>
<tr>
<td>8</td>
<td>W</td>
<td>36</td>
<td>17 Optic neuritis</td>
<td>MD/1</td>
<td>MD/1.2</td>
<td>MD/27 18.6/40</td>
<td>MD/59.4</td>
</tr>
<tr>
<td>9</td>
<td>W</td>
<td>44</td>
<td>32 Optic neuritis</td>
<td>0/.13</td>
<td>0/.17</td>
<td>0/.26 1/10</td>
<td>50/23</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>74</td>
<td>125 AION</td>
<td>MD/.9</td>
<td>MD/8</td>
<td>MD/24 5.7/10</td>
<td>MD/37</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>67</td>
<td>23 AION</td>
<td>.06/.04</td>
<td>.17/.0</td>
<td>15/0 4.3/9</td>
<td>47.9/43</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>28</td>
<td>24 Idiopathic ON atrophy</td>
<td>1.25/.02</td>
<td>1.2/0</td>
<td>27/0 13/1</td>
<td>31/10</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>66</td>
<td>78 Glaucoum</td>
<td>5/0</td>
<td>.6/0</td>
<td>24/0 17/0</td>
<td>57/16</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>68</td>
<td>163 Central retinal vein occlusion</td>
<td>.9/.05</td>
<td>.8/.12</td>
<td>23/2 12/4</td>
<td>58/39</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>47</td>
<td>64 NAION</td>
<td>.05/1</td>
<td>0/1.5</td>
<td>0/26 3/5</td>
<td>33/45</td>
</tr>
<tr>
<td>17</td>
<td>M</td>
<td>53</td>
<td>6 AION</td>
<td>0/.6</td>
<td>0/.6</td>
<td>0/21 0/6</td>
<td>0/40</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>57</td>
<td>14 Idiopathic optic atrophy</td>
<td>.25/.25</td>
<td>.4/.4</td>
<td>21/23 13/13</td>
<td>59/60</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>63</td>
<td>60 AION</td>
<td>.7/8</td>
<td>.8/8</td>
<td>27/23 18/8</td>
<td>53/50</td>
</tr>
</tbody>
</table>
Fig. 1 – Analysis of temporal dynamics of synchronization. (A) Filtered alpha band oscillations are plotted in grey. An envelope of oscillations (in blue) was used as an index of synchronization strength. Note that healthy control, patient, and surrogate data exhibit different amplitudes. (B) For analyses of temporal dynamics envelopes were normalized by subtracting temporal mean and dividing by temporal STD. For analysis of active- and waiting-periods for each envelope we set an upper and lower threshold (65th and 35th percentile, in green and magenta respectively). Every time the signal went beyond the upper threshold or below the lower threshold we assume it entered an active- or waiting-period, respectively. (C) Cumulative distributions of active-/waiting-periods’ duration were created and 90th percentile was taken as a measure of active-/ waiting-periods duration. (D) A second measure, HFD, indicates the tendency of the time series to fill the space between a straight line (HFD = 1) and a plane (HFD = 2). (E) The third measure, DFA exponent, quantifies long-range temporal correlations in the envelopes, with higher values indicating stronger, more complex temporal correlations. High-alpha band activity of control subjects was characterized by occurrence of long active- and waiting-periods (C), lower HFD (D), and higher DFA exponents (E).
connectivity between electrodes estimated by phase locking value (PLV; Lachaux, Rodriguez, Martinerie, & Varela, 1999). To obtain amplitude envelopes absolute values were taken from Hilbert-transformed signals. PLV, which measures variability of phase difference in a time interval, was calculated as follows:

$$PLV_t = \frac{1}{N} \sum_{n=1}^{N} \exp(i(\psi_{\text{chan}1} - \psi_{\text{chan}2}))$$

where N is the number of time points in a time window t, \(\psi\) denotes phase from a given channel at a time-point n, and i is the imaginary unit.

PLV were calculated using a sliding window of 601 points (300 msec) length which was shifted one point at a time to obtain maximal temporal resolution. To obtain estimates of PLV time courses for each electrode, time courses of PLV between n and all other electrodes were averaged.

The mean amplitude of oscillations and PLV (Figs. 2A and 3A) were calculated as time-averaged amplitude envelope and time-averaged PLV.

2.3.4. Surrogate data
Filtering causes temporal integration of the signal and therefore might induce temporal correlations even in non-correlated time series. To control for this effect, white noise time-series of length equal to the analyzed EEG signals were created. To obtain surrogate data for alpha I and alpha II white noise was filtered with a band-pass FIR filter with cut-off and filter order the same as used for EEG data (7–9 Hz and 142 points for alpha I; 11–13 Hz and 90 points for alpha II). Filtered white noise was Hilbert transformed to obtain amplitude envelopes which were analyzed with three analysis methods described below.

2.3.5. Analysis of synchronization dynamic
All the methods used to study dynamic of amplitude/PLV time series were independent from time series amplitude. This way we were able to obtain biomarkers independent from the ones reported in our previous study where weaker amplitude/coherence of alpha oscillations in patients was already described (Bola et al., 2014).

2.3.5.1. Synchronization stability. Processing of information in the brain requires both flexibility and stability. To quantify temporal stability of synchronization we studied the periods when the brain lingers in a state of strong or weak synchronization (see: Montez et al., 2009; Figs. 2B, C and 3B, C). To this end for each time series two thresholds, lower and upper, were set based on percentile values. Lower threshold was defined as 35th percentile and upper as 65th percentile. All values above the upper threshold were considered to belong to an “active-period” (strong synchronization) and all values below the lower threshold were considered to belong to a “waiting-period” (weak synchronization). Length of each synchronized- and waiting-period was calculated and their cumulative distributions calculated. In agreement with Montez et al. (2009), we noticed that the probability to linger in an active-/waiting-period was greater for EEG time series than for created surrogate data. In other words, the probability distribution obtained from EEG had a slowly decaying, long tail. Therefore, for each time series the 90th percentile of the active-/waiting-periods length was taken as an index of lingering time. By taking the 90th percentile we were able to capture the slowly decaying tail of the distribution. Repeating the analysis with different threshold values (e.g., 50th percentile lower and 50th percentile upper, 25th percentile lower and 75th percentile upper) led to similar between groups differences.

2.3.5.2. Higuchi Fractal Dimension (HFD). The complexity of a signal was quantified using HFD (Higuchi, 1988; Figs. 2D and 3D). This method has been used to estimate dimensional complexity of physiological signals, including EEG (Accardo, Affinito, Carrozzzi, & Bouquet, 1997). The mathematical details of the method can be found here (Higuchi, 1988). Briefly, HFD may be illustrated by the tendency of the time series to fill the space between a straight line (HFD = 1) and a plane (HFD = 2). Therefore a flat line, or a low frequency sine wave, is characterized by HFD ≈ 1 and white noise by HFD ≈ 2.

2.3.5.3. Detrended fluctuation analysis (DFA). Finally, DFA was used to quantify long-range temporal correlations in synchronization time series (Figs. 2E and 3E). DFA has been introduced by Peng et al. (1994) and used to analyze long-range temporal correlations in non-stationary physiological time series, including EEG power envelopes and functional connectivity (Linkenkaer-Hansen et al., 2001; Stam & de Bruin, 2004). When calculating DFA we followed the pipeline proposed by Hardstone et al. (2012). Briefly, for each time series [x] we calculated the cumulative sum to obtain time series profiles [xcum]. A set of time windows was defined and for each window size [l] the signal profile was divided into a set of separate segments [u] of length equal to the window size [l]. Segments were created with 50% overlap. Each signal segment [u] was detrended using least-squares fit [wdetrend]. STD of the detrended segment was calculated (\(\sigma(w_{\text{detrend}})\)). Fluctuation function was defined as mean STD for segments of the same size [F(t) = mean(\(\sigma(w_{\text{detrend}})\))]. F was plotted for all windows sizes on logarithmic axes. The DFA exponent is the slope of the trend line and is estimated using linear regression. DFA exponent indicates whether a time series is anti-correlated (DFA<.5), uncorrelated (DFA = .5), positively correlated (DFA>1), or scale-free (DFA>1). The smallest window for analysis of amplitude envelopes was estimated to be 300 points based on procedure described by Hardstone et al. (2012) and it was used as the smallest window also in the PLV analysis.

2.3.6. Amplitude matched data
To prove that between-groups differences in temporal dynamics were not due to between-groups differences in amplitudes, we created an amplitude-matched data set (Fig. 4). In this analysis we focused on O1 and O2 electrodes. For every subject we divided the 60 sec long signal into 10 equal epochs. To obtain a data set without differences in amplitude between controls and patients 5 epochs with the lowest amplitude were chosen in case of controls, while 5 epochs with highest amplitude were chosen in case of patients. We calculated HFD on the chosen epochs and compared between groups. This control analysis was done using HFD as, unlike
2.4. Statistical analyses

Initially between groups comparisons were conducted separately for each electrode (see topographic maps in Figs. 2 and 3). Then, for each frequency band, data were averaged over electrodes with significant between groups difference and plotted in a scatter plot. In several cases there was no electrode showing significant between-groups differences in the alpha I band. Then the same electrodes as for alpha II were taken to create alpha I scatter plots. Another statistical test was conducted on electrodes-averaged data and results of this final test are reported in the results section.

Before conducting between-groups statistical tests normality of distribution was assessed with Kolmogorov-Smirnov test. If measures of both groups exhibited normal distribution an independent sample t-test was used. Otherwise, Mann-Whitney U-test was used. To assess the relationship between EEG and clinical variables, Pearson correlation coefficient was used. A criterion of $p = .05$ (two-tailed) was set for all statistical tests. Results are reported as mean ± standard error of the mean (SEM).

3. Results

3.1. Synchronization strength

Patients exhibited lower power of alpha II band ($z = 2.07, p = .038; \text{Fig. 2A}$) and weaker alpha II functional connectivity ($z = 2.03, p = .042; \text{Fig. 3A}$) indicating that strength of both, local and global (distant) neural synchronization is disturbed.

3.2. Temporal stability of synchronization: active- and waiting-periods

Patients exhibited disturbed temporal dynamic of neural synchronization in the alpha II band. The probability of long active-periods ($z = 2.41, p = .015; \text{Fig. 2B}$) and long waiting-periods ($z = 2.53, p = .011; \text{Fig. 2C}$) was significantly lower in patients than in control subjects in alpha II band. This indicates that synchronization in patients is more volatile, with shorter periods of stable strong/weak synchronization.

This is confirmed by PLV, which also indicates lower probability of long active-periods ($z = 2.30, p = .021; \text{Fig. 3B}$) and waiting-periods ($z = 2.83, p = .004; \text{Fig. 3C}$) in the alpha II band. Yet, we also noticed that two electrodes (CP5, FC6) showed higher probability of long synchronized-periods in the alpha I band in patients ($z = 2.18, p = .028$).

Fig. 2 – Amplitude (A) and temporal dynamics (B–E) of local neural synchronization. Topographic plots show values of calculated measures for all electrodes. Electrodes at which significant between-groups difference was found are marked in red (third column). On the right side the scatter plots present data from all subjects. To create scatter plots data were averaged over all electrodes showing significant between-groups difference and retested statistically. The thick horizontal line indicates mean and thin horizontal lines indicate standard error of the mean (SEM).
Distant synchronization (PLV)

A) PLV strength

B) Active-periods

C) Waiting-periods

D) Higuchi Fractal Dimension (HFD)

E) Detrended Fluctuation Analysis (DFA)

Fig. 3 – Strength (A) and temporal dynamics (B–E) of distant neural synchronization (PLV). Conventions are the same as in Fig. 2.
3.3. HFD

Further evidence for altered temporal dynamic of neural synchronization in patients comes from HFD analysis. Time-series representing alpha II amplitude in patients were characterized by higher HFD \((z = 2.99, p = .002; \text{Fig. 2D})\). Similarly, PLV time series from patients exhibited higher HFD than those in control subjects \((z = 2.26, p = .023; \text{Fig. 3D})\). A higher HFD points towards a more random, noise-like character of synchronization dynamics in patients.

3.4. DFA

Finally, the third method quantifying temporal correlations in time-series, DFA, also indicates weaker temporal patterns in patients data. Specifically, alpha II amplitude envelopes were characterized by lower DFA exponents in patients \((z = 2.76, p = .005; \text{Fig. 2E})\). However, at a single electrode (FC1) the alpha I DFA exponent was higher in patients group \((z = 1.99, p = .046)\).

Weaker temporal correlations in alpha II synchronization were found also for PLV time-series \((z = 2.60, p = .009; \text{Fig. 3E})\). Therefore, in line with two other methods used, DFA analysis indicates that dynamics of synchronization in patients exhibits weaker temporal correlations and more noise-like character.

3.5. Comparison to surrogate data

The three methods used to study temporal patterns were applied to surrogate data, being filtered white noise, where no true temporal structure was expected. All three methods indicate that in patients temporal dynamic of alpha II power is similar to temporal dynamic of white noise \((\text{Fig. 2B, C, D, E})\). This indicates that alpha II synchronization pattern in patients possess no temporal structure, or the pattern exhibits a very random, noise-like character.

3.6. Amplitude-matched data

Although, from a mathematical point of view, the three methods used were by definition amplitude-independent, from the physiological point of view it is still possible that a decrease in alpha power is tightly linked to changes in the temporal network structure in patients. Therefore, we sought further confirmation that between-groups differences in temporal dynamic cannot be accounted for by differences in power. To this end we created amplitude-matched datasets by choosing epochs with high mean amplitude for patients and low mean amplitude for controls (see: methods section). In this way we were able to confirm that disturbance of temporal dynamics of alpha II in patients \((z = 2.45, p = .014; \text{Fig. 4})\) is independent of power decreases.

3.7. Correlations with vision measures

Alpha band oscillatory activity was related to visual capabilities of patients as measured by perimetry \((\text{Fig. 5})\). Higher amplitudes in the alpha II band were related to better detection abilities in static perimetry \((r = .52, p = .021)\). But also measures of temporal dynamic were related to patients’ vision. Specifically, a larger visual field as assessed by kinetic perimetry was associated with longer waiting-periods \((r = .47, p = .041)\), whereas better detection in static perimetry was related to both, lower HFD \((r = -.54, p = .017)\) and longer waiting-periods \((r = .54, p = .014)\). We did not find correlations between PLV and vision measures.

4. Discussion

Loss of vision caused by the visual system damage leads to structural and functional alterations in downstream visual system structures \(\text{review: Gupta & Yücel, 2007; Merabet & Pascual-Leone, 2009; Sabel, Henrich-Noack, Fedorov, & Gall, 2011; Wandell & Smirnakis, 2009.}\) The majority of prior studies on the lesion-induced visual system plasticity investigated changes in the structures located at the early stages of the visual pathway, e.g., LGN and V1. But not much is known about the possible changes on the level of brain cortical networks. We hypothesized that prolonged deafferentation might disturb synchronization of visual networks and that this is manifested also in the resting-state. Providing such network effects can be found, we expected resting-state synchronization to be related to perceptual capabilities of patients, i.e., that impaired synchronization would be associated with greater vision loss.

Indeed, temporal patterns of spontaneous neural synchronization were found to be disturbed in patients with pre-chiasmatic (i.e., retinal and/or optic nerve) visual system damage. Specifically, in line with our previous study of resting-state functional connectivity \(\text{(Bola et al., 2014,)}\), we found changes in the high-alpha band activity (alpha II; 11–13 Hz). In patients temporal patterns of high-alpha band synchronization exhibit less complex, more random and noise-like structure. Importantly, greater complexity of spontaneous alpha synchronization was related to better performance in visual detection tests.
4.1. Spontaneous activity of large-scale brain networks provides a window into brain functioning

Why do we study spontaneous activity of large-scale networks in brain damage patients? The current view is that task-related processing merely modifies (perturbs) the spontaneous network activity and therefore spontaneous activity patterns constitute a good predictor of perception and action (Harmeilech & Malach, 2013). Indeed, in patients suffering from motor or attentional impairments caused by stroke, the resting-state activity and functional connectivity predict the behavioral capabilities (Assenza, Zappasodi, Pasqualetti, Vernieri, & Tecchio, 2013; Carter et al., 2010; Castellanos et al., 2010; Ferreri, Ponzo et al., 2014; Ferreri, Vecchio, Ponzo, Pasqualetti, & Rossini, et al., 2014; He, Shulman, Snyder, & Corbetta, 2007; Tecchio et al., 2005, 2007). Further, spontaneous EEG activity was recently shown to be altered in congenitally blind subjects (Hawellek et al., 2013). Therefore, here we used the resting-state paradigm to characterize network activity in vision loss patients.

In the present study resting-state activity was recorded while subjects were keeping their eyes closed. It is well-established that the visual system is not silent at rest but that brain visual circuits generate rhythmic oscillations in the 7–13 Hz range called alpha rhythm (review: Hughes & Crunelli, 2005). Thus, studying resting-state alpha band synchronization might be a reasonable mean to probe functioning and efficiency of the visual system requiring no overt visual task. As expected, between-groups differences were found mainly (but not only) at the occipital/parietal regions where brain areas responsible for vision are located (see: topological maps in Figs. 2 and 3). Importantly, we recorded “eyes-closed” EEG in a dark room so that any between-groups differences could not be attributed to differences in the degree of visual input (which is reduced in patients) during EEG recording.

Several studies indicate that the classically defined alpha band (7–13 Hz) is not a homogeneous phenomenon but that it should be divided into low-alpha (alpha I) and high-alpha (alpha II), which play different functional roles (Klimesch, 1999). Indeed, we revealed that only high-alpha band functional connectivity is impaired in patients with vision loss (Bola et al., 2014), which is why here the two alpha sub-bands were analyzed separately. But instead of analyzing spatial patterns of functional connections as in our previous work (Bola et al. 2014) we now focused on the temporal aspects of alpha band activity.

4.2. Temporal aspect of brain networks synchronization

Brain activity exhibits complex spatio-temporal properties. Most of the hitherto conducted neuroimaging studies focused on how the spatial representation of the visual field changes after damage (review: Wandell & Smirnakis, 2009). Yet, neural processes must be coordinated not only in space but also in time. Therefore, loss of temporal complexity – or any deviation from the optimal temporal pattern – might be indicative of changes in the underlying neural circuits and cause behavioral deficits. Indeed, temporal complexity is reduced in various brain disorders such as depression (Linkenkaer-Hansen et al., 2005), Alzheimer’s disease (Montez et al., 2009), schizophrenia (Nikulin et al., 2012), epilepsy (Monto et al., 2007), and stroke (Zappasodi et al., 2014).

Because the subjects studied here suffered from pre-chiasmatic (peripheral) lesions, but the cortex itself was not injured, we assume that the observed disturbance of...
spontaneous synchronization is a diaschisis effect. Diaschisis is defined as neurophysiological changes that occur distant to a focal brain lesion, i.e., a deafferentation depression (von Monakow, 1914; review: Carrera & Tononi, 2014; Catani et al., 2012). To our knowledge, this is the first study indicating that not only strength of activity and functional connectivity, but also temporal patterns of activation affect behavior and are signs of diaschisis. Crucially, in the present study temporal complexity of alpha synchronization was related to patients’ perceptual capabilities: higher complexity was associated with better vision. This is in line with the hypothesis that greater temporal complexity, indicating system’s greater flexibility, is advantageous for the function (Garrett et al., 2013; Goldberger et al., 2002).

Concerning the role of alpha activation in vision one should note that although resting-state alpha-band was related to perceptual capabilities, we do not claim a special (exclusive) role of the alpha band for perception. Rather we argue that the alpha activity, being the most widespread rhythm in the visual system at rest, provides a biomarker of the visual system’s structural and functional integrity. Yet, in other functional states different rhythms might constitute such biomarker as well, e.g., during perception gamma might be an indicator of visual system’s integrity (Schadow et al., 2009). Thus, future studies need to elaborate on this issue and possibly employ tests of higher visual functions, e.g., shape or motion discrimination, or feature binding tasks to fully comprehend more complex features of visual perception.

### 4.3. Network synchronization and perception: areas of residual vision (ARV)

How can the relationship between network synchronization and vision impairments be explained? It has been shown that the instantaneous network state might change responsiveness of brain areas (Ferreri, Ponzo et al., 2014; Ferreri, Vecchio et al., 2014) and determine perception thresholds (Babiloni, Vecchio, Bultrini, Romani, & Rossini, 2006; Hanslmayr et al., 2007; Van Dijk, Schoffelen, Oostenveld, & Jensen, 2008; Weisz et al., 2014) and reaction time (Vecchio et al., 2014). The effect of the network state on perception can be mainly observed under difficult perceptual conditions, when the stimulus is weak and noisy, with poor signal-to-noise ratio (e.g., a stimulus at threshold, an incomplete figure etc.). Because in patients the visual input is permanently reduced and/or noisy, we propose that the network state plays a key role in patients’ perception. Our findings indicate that in patients the network state is suboptimal for input processing, as indicated by disturbed synchronization and functional connectivity. This might hamper perception even beyond the direct effect of the anatomical damage.

Importantly, in patients with pre-chiasmatic visual system damage the visual field defect is typically not clear-cut, but there are extensive “ARV” (Sabel, Henrich-Noack et al., 2011). In ARVs, also known as “relative defects”, residual perception is still present but it is unreliable and imprecise (increased contrast thresholds, slowed reaction times, reduced acuity etc.). It was proposed by us earlier that ARVs likely correspond to the partially damaged areas of the retina or optic nerve (Sabel, Henrich-Noack et al., 2011). Therefore, when stimuli are presented in ARVs, the bottom-up signal reaching visual cortex might have a poor signal-to-noise ratio and instantaneous state of the cortical networks might now play a greater role than it would in normal subjects. Consequently, permanently disturbed neural synchronization in patients might aggravate vision loss in ARVs. Yet, this hypothesis needs to be tested directly by future studies.

The importance of the network-state and top-down influences for patients’ vision was demonstrated by behavioral studies investigating the role of spatial attention in ARV perception. Detection in ARV was improved when attention was cued to the location of presentation before the stimulus onset (Poggel, Kasten, Müller-Oehring, Bunzenthal, & Sabel, 2006). Attention training has also prolonged effects on perception and plasticity as vision restoration training combining stimulus presentations (bottom-up input) with attentional cuing (top-down influence) is more effective than the training without the attentional cuing (Poggel, Kasten, & Sabel, 2004). Finally, a recent fMRI study found that perceptual training alters brain activity beyond the visual areas, specifically in the right temporoparietal junction (TPJ), which is a key node in the attention network (Lu, Li, Wang, Zhou, Wei, Sabel, unpublished observation). This is in line with the view that attention and the instantaneous network state strongly modulate perception under difficult perceptual conditions.

This raises the question whether the network functional state is related to visual capabilities per se, or rather to the attentional state or vigilance moderating the effect. Indeed, attention has been shown to affect synchronization within brain visual network (Siegel, Donner, Oostenveld, Fries, & Engel, 2008). Thus, distinguishing between network state and attention is difficult because the actual network state determines attention, and vice versa. Here we do not aim to propose the specific mechanism of network desynchronization in patients. We rather propose that not only the anatomical features matter to understand vision loss, but that also the state of brain functional networks have to be considered. Possible attentional problems in patients might be both, the cause and the effect of disturbed networks state. Future neuroimaging studies are needed to more precisely define the mechanism of network top-down modulation impairments and their role in vision loss.

### 4.4. Network synchronization and perception: “sightblindness”

Furthermore, if the large-scale networks are in a suboptimal state perception may be affected in a non-retinotopic manner, i.e., affecting the whole visual field, including presumably “intact” regions. Indeed, previous studies demonstrated that patients with localized vision loss (scotoma) experience perceptual impairments even in the intact visual field areas distant from the scotoma. Specifically, the areas considered to be “intact” based on the perimeter results actually exhibit subtle perceptual deficit in the processing speed (Bola, Gall, & Sabel, 2013b; Cavézian et al., 2010; Poggel, Treutwein, & Strasburger, 2011) and contour integration (Paramei and Sabel, 2008; Schadow et al., 2009). These subtle deficits in the “intact” field are “sightblind” (review: Bola, Gall, & Sabel,
2013a), as they are the flip-side of “blindisight” where subtle residual vision exists deep in the “blind” field. The “sightblind” effect was found in patients with post-chiasmatic damage (e.g., Poggel et al., 2011), but also in patients with pre-chiasmatic lesions (e.g., Bola et al., 2013a). As previously shown, intact field deficits are related to the brain functional state, as slower reaction-time in the intact visual field sectors was associated with weaker resting-state functional connectivity (Bola et al., 2014). Interestingly, perceptual deficits might include other domains, beyond vision, as glaucoma patients suffer from auditory processing deficits as well (Rance et al., 2012), and this might be an expression of a global, network-wide disturbance of synchronization. Importantly, “sightblindness” can be reversed by vision training (Poggel, Treutwein, Sabel, & Strasburger, 2015).

4.5. Network synchronization as a target for vision restoration treatments

If future studies confirm that network synchronization is one of the factors affecting patients’ perception, then improving such synchronized network activity might be one avenue towards vision restoration. Indeed, patients’ vision can be improved using non-invasive brain stimulation techniques, e.g., repetitive transorbital alternating current stimulation (rTACS) that sends pulsed currents to the retina and brain, (Gall et al., 2011; Sabel, Fedorov et al., 2011; Schmidt et al., 2013). The postulated mechanism of action of rTACS is re-synchronization of visual circuits (Bola et al., 2014). But the network state might be also modified by direct current stimulation (Flow, Obretenova, Fregni, Pascual-Leone, & Merabet, 2012) and neurofeedback training (Nan, Wan, Lou, Vai, & Rosa, 2013).

4.6. Conclusions

Lesions of the visual pathway lead to vision loss by reducing bottom-up input to visual cortex. But as we and others show there are also indirect consequences as prolonged vision loss (sensory deprivation), namely a disturbance of global brain networks. Therefore, we propose that patients’ vision is impaired due to both: (i) reduced visual input (anatomical damage) and (ii) disturbed visual brain networks which are in a suboptimal (insufficiently synchronized) state for input processing. Thus, vision loss should be understood as a combination of both, the anatomical damage (deafferentation) and the functional network disturbance.

Competing interests

The authors declare no competing interests.

Acknowledgments

The study was supported by Otto-von-Guericke University of Magdeburg (LOM fellowship to MB) and by the BMBF network ERA-net Neuron “Restoration of Vision after Stroke (REVIS)” grant (nr 01EW1210) to BAS.

REFERENCES


is not specific to the “preferred retinal locus”. Journal of Neuroscience, 29(9), 2768–2773.
cortical stimulation. Neururehabilitation and Neural Repair, 26(6), 616–626.