Brain functional connectivity network breakdown and restoration in blindness

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ABSTRACT

Objective: To characterize brain functional connectivity in subjects with prechiasmatic visual system damage and relate functional connectivity features to extent of vision loss.

Methods: In this case-control study, resting-state, eyes-closed EEG activity was recorded in patients with partial optic nerve damage (n = 15) and uninjured controls (n = 13). We analyzed power density and functional connectivity (coherence, Granger causality), the latter as (1) between-areal coupling strength and (2) individually thresholded binary graphs. Functional connectivity was then modulated by noninvasive repetitive transorbital alternating current stimulation (rtACS; 10 days, 40 minutes daily; n = 7; sham, n = 8) to study how this would affect connectivity networks and perception.

Results: Patients exhibited lower spectral power ($p = 0.005$), decreased short- ($p = 0.015$) and long-range ($p = 0.033$) coherence, and less densely clustered coherence networks ($p = 0.025$) in the high-alpha frequency band (11–13 Hz). rtACS strengthened short- ($p = 0.003$) and long-range ($p = 0.032$) alpha coherence and this was correlated with improved detection abilities ($r = 0.57$, $p = 0.035$) and processing speed ($r = 0.56$, $p = 0.049$), respectively.

Conclusion: Vision loss in the blind is caused not only by primary tissue damage but also by a breakdown of synchronization in brain networks. Because visual field improvements are associated with resynchronization of alpha band coherence, brain connectivity is a key component in partial blindness and in restoration of vision. ***Neurology*® 2014;83:1–10**

GLOSSARY

AOI = area of interest; **GC** = Granger causality; **HRP** = high-resolution perimetry; **IAF** = individual alpha frequency; **NEI-VFQ** = National Eye Institute Visual Function Questionnaire; **RT** = reaction time; **rtACS** = repetitive transorbital alternating current stimulation.

Damage to visual pathway structures results in vision loss in the visual field sector retinotopically corresponding to the damaged tissue and consequently leads to marked impairments in quality of life.[1] Vision loss is thus viewed as the result of local tissue damage and malfunction in the region of primary deafferentation. However, visual system structures interact with various brain areas that all act in concert to create the subjective perceptual experience.[2] Therefore, local brain lesions might have more widespread consequences, possibly disturbing synchronization of widely distributed visual networks which, in turn, might further hamper perception. Such effects of distributed brain networks on motor or cognitive capabilities were already reported.[3–5]

To address the issue of the role of a widely distributed neuronal network in vision loss, we studied brain functional connectivity networks in subjects with peripheral optic nerve lesions that lead to partial blindness. We wished to address 2 research questions. First, do peripheral lesions, which do not directly damage the visual cortex, permanently alter spontaneous cortical activity? Network disturbances reaching regions beyond the area of primary deafferentation have already been observed in the motor system.[6–8] Second, are features of the connectivity network related to patients' perceptual capabilities? To this end, patients with visual system damage were compared to uninjured controls to define potential markers of vision loss. Further, as alpha band connectivity was found to be disturbed in patients, we utilized noninvasive brain

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stimulation to restore alpha band synchronization[9–11] and studied its effects on perceptual functioning.

METHODS For details of the methods, see e-Methods on the *Neurology*® Web site at Neurology.org.

Standard protocol approvals, registrations, and patient consents. The study was approved by an ethical standards committee on human experimentation (institutional) and written informed consent was obtained from all patients participating in the study (consent for research). All patients were treated according to the Declaration of Helsinki.

Subjects and study design. The case-control study design was used. The study sample consisted of 15 patients (table e-1) with chronic prechiasmatic visual system damage and 13 age-matched control subjects without any neurologic dysfunctions. Subjects were recruited and tested from November 2006 to March 2010 in Magdeburg, Germany. For the noninvasive brain stimulation experiment, patients were randomly assigned to either a sham (n = 8; 1 excluded) or verum group (n = 7). The groups did not differ at baseline with respect to demographic and vision-related measures.

All patients were tested with perceptual tests and EEG before and after 10 days of daily noninvasive brain stimulation (baseline and post, respectively). Measurements were done 1 or 2 days before the first and after the last stimulation session. Baseline data from patients were compared to data from healthy control subjects.

Vision tests. Visual acuity was measured 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. Visual fields of patients were mapped with static and kinetic perimetry (Twinfield Perimeter, Oculus, Lynnwood, WA) and with computer-based high-resolution perimetry (HRP; figure e-1). All tests were conducted monocularly and vision measures were averaged for both eyes when correlating with EEG measures. To quantify subjective vision, patients filled out the National Eye Institute Visual Function Questionnaire 39 (NEI-VFQ), and a composite score, excluding the "general health" subscale, was calculated. Vision diagnosis was done by a person unaware of the group assignment (sham or repetitive transorbital alternating current stimulation [rtACS]) of the patients.

Noninvasive brain stimulation protocol. rtACS was applied daily for 10 days (40 minutes each) with 4 electrodes attached to the skin near the eyeballs ("transorbitally"). Current amplitude and frequency range were individually adjusted for every subject and session. Current strength was selected to be clearly above (125%) phosphene thresholds as reported by the patients. The neurologist applying rtACS and recording EEG was not blinded to group assignment (sham or rtACS) of the patients, as this was technically not possible.

EEG recordings and analysis. All subjects were seated in a dimly lit room and instructed to keep their eyes closed during the whole recording session. EEG was acquired with 30 electrodes placed according to 10-10 system. EEG data analysis was carried out in MatlabR2011b and EEGlab.[12] After standard preprocessing, spectral density was calculated for each channel and presented as 10log10 values. We investigated spectral power at 2 areas of interest (AOIs): occipital (O1, O2) and frontal (FC1, Fz, FC2).

For the EEG analysis, we defined 5 spectral bands: delta, 1–3 Hz; theta, 3–7 Hz; low alpha (alpha I), 7–11 Hz; high alpha (alpha II), 11–14 Hz; and beta, 14–30 Hz.

Coherence was calculated for each pair of channels as an indicator of functional connectivity. Coherence was averaged over frequency bins to give an estimate for defined EEG bands. We analyzed: (1) short-range coherence within the occipital AOI (between O1 and O2); (2) short-range coherence within the frontal AOI (between FC1, FC2, Fz); and (3) long-range coherence between occipital and frontal AOI (between [O1, O2] and [FC1, FC2, Fz]).

Long-range connectivity between occipital and frontal AOI was additionally assessed with Granger causality (GC), a directed measure of functional interactions. This permitted us to confirm our initial result with an independent method and to test the hypothesis concerning the direction of the influence. A freely available Matlab toolbox[13] was used to calculate GC.

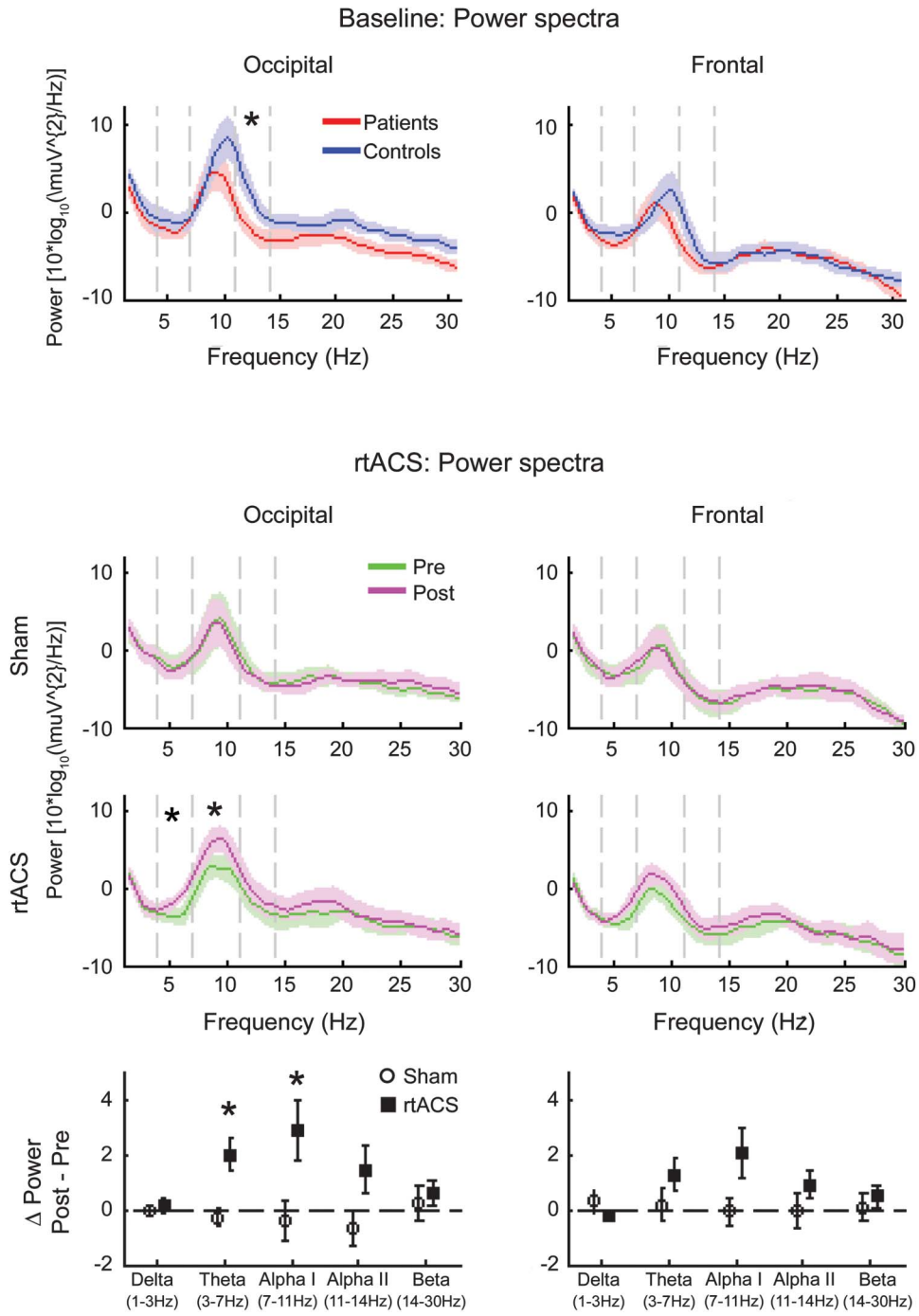
Graphs analysis. To analyze topology of the functional connectivity networks for every subject and EEG band coherence, results were represented as binary graphs containing the same number of connections. "Small-world" measures—clustering coefficient and characteristic path length[14]—were calculated for each graph and compared between groups and conditions.

Statistical analyses. Data were analyzed in 2 steps. First, a repeated measures analysis of variance model was applied to capture the effect of different factors on EEG measures. Second, detailed between-group comparisons were conducted with independent samples *t* test. The effects of rtACS on EEG measures were analyzed as post-rtACS changes (ΔEEG = EEGpost−EEGpre). To assess the relationship between EEG and clinical variables, Spearman correlation coefficient was used. All statistical significance tests used the criterion of $p = 0.05$ (2-tailed). Analyses were done in MatlabR2011b and SPSS 21 and displayed as mean ± SEM.

RESULTS **Power spectra.** Patients exhibited lower spectral power than healthy controls, and the between-group difference depended on the area of interest (group × AOI interaction: $F_{1,24} = 7.25$, $p = 0.012$; figure 1). Specifically, alpha II band power at the occipital AOI was lower in patients than in controls ($t_{1,26} = 2.60$, $p = 0.015$). Furthermore, after rtACS, the change in spectral power was greater in the rtACS group than in the sham group, which was dependent on AOI (group × AOI interaction: $F_{1,10} = 6.20$, $p = 0.026$) and frequency band (group × band interaction: $F_{4,4} = 3.48$, $p = 0.034$). Detailed comparisons showed that rtACS led to an increase of theta ($t_{1,12} = 3.35$, $p = 0.006$) and alpha I power ($t_{1,12} = 2.52$, $p = 0.027$) at the occipital AOI.

Short-range functional connectivity. Patients had lower short-range coherence than control subjects, and the difference depended on the frequency band (group × band interaction: $F_{4,18} = 3.46$, $p = 0.044$; figure 2). Between-group comparisons indicate that alpha II coherence at the frontal AOI differed between groups ($t_{1,26} = 3.17$, $p = 0.004$). After rtACS, greater increase in short-range coherence was observed in the rtACS group than in the sham group and the effect was dependent on the frequency band (group × band interaction: $F_{4,4} = 3.36$, $p = 0.017$). Specifically, alpha I coherence increased at the frontal AOI in the rtACS group ($t_{1,12} = 3.71$, $p = 0.003$).

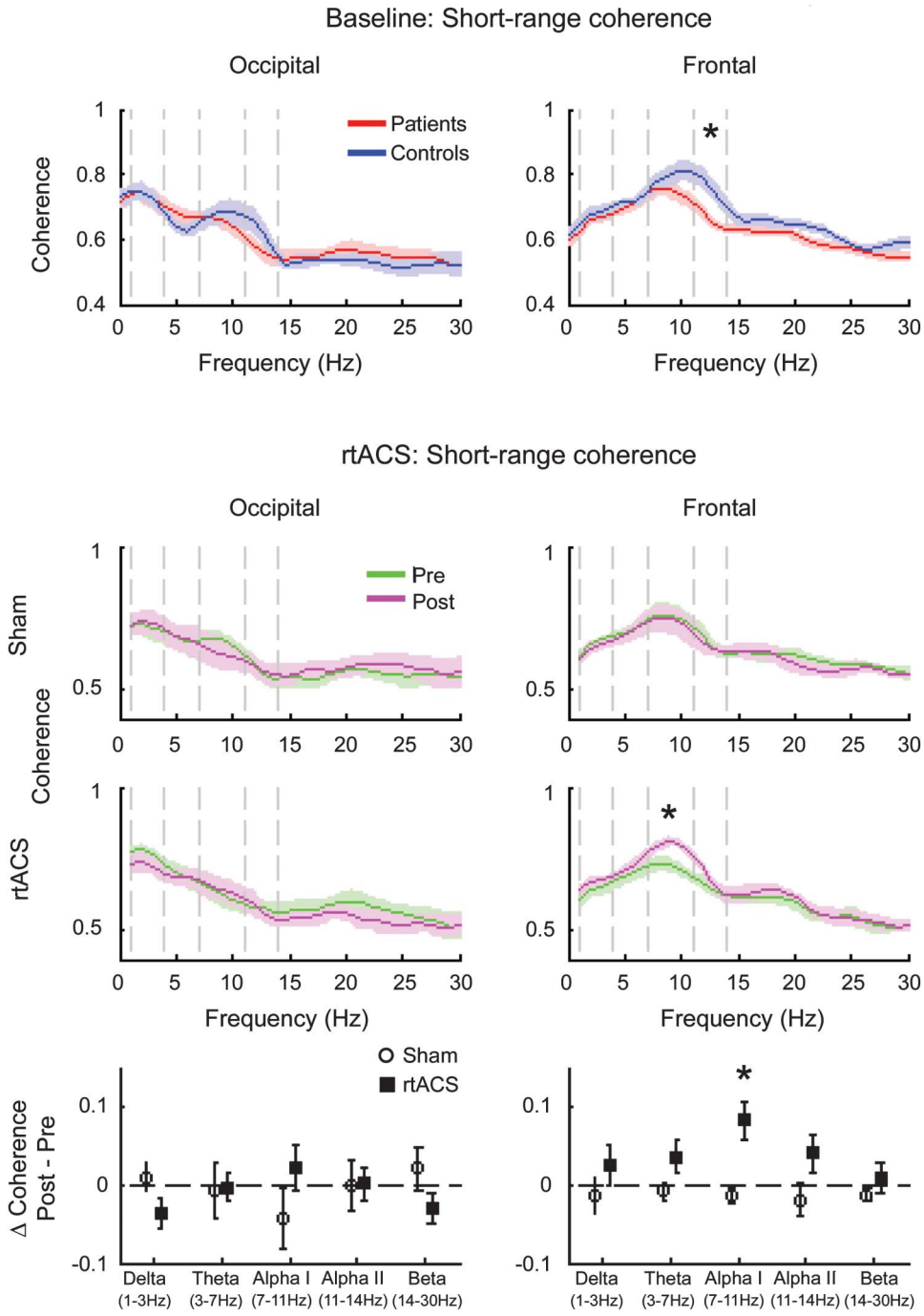
Figure 1 Baseline and post-rtACS power spectra



Baseline analysis indicates that patients exhibit lower power of alpha II band than control subjects. This was found at the occipital (O1, O2) area of interest (AOI) but not at the frontal AOI (FC1, FC2, Fz). Further, 10-day rtACS stimulation induced theta and alpha I entrainment at the occipital location. Gray vertical lines indicate chosen frequency bands. rtACS = repetitive transorbital alternating current stimulation.

Long-range functional connectivity. Long-range coherence was lower in patients than in control subjects, and the effect depended on frequency band (group × band interaction: $F_{4,18} = 3.79$, $p = 0.35$). Detailed analysis showed that patients had lower long-range coherence in the alpha II band than control subjects ($t_{1,26} = 2.20$, $p = 0.042$; figure 3). Analysis of GC—a directed measure of functional interactions—demonstrated that long-range functional interactions were weaker in patients than in healthy controls (group: $F_{1,26} = 4.49$, $p = 0.44$); specifically, patients had weaker occipital-to-frontal connectivity in the delta band ($t_{1,26} = 2.18$, $p = 0.045$).

Figure 2 Baseline and post-rtACS short-range coherence

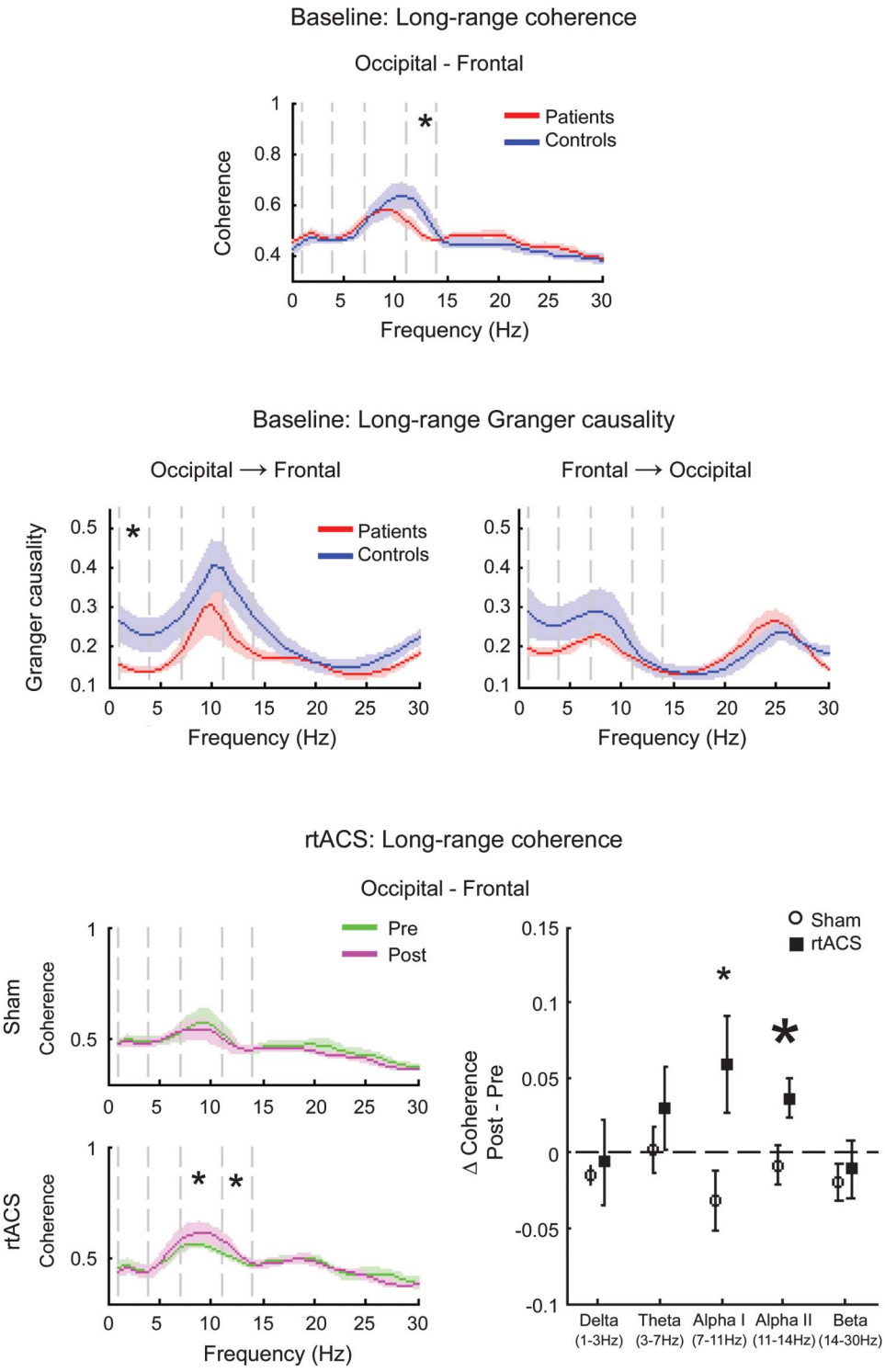


Short-range coherence was defined as coherence within occipital (O1, O2) or frontal (FC1, FC2, Fz) areas of interest (AOIs). In the frontal AOI, patients had lower alpha II coherence than control subjects. Further, 10-day rtACS stimulation increased short-range coherence in the alpha I band in the frontal AOI. rtACS = repetitive transorbital alternating current stimulation.

Analyzing the effects of rtACS, we found that neither the group effect (group: $F_{1,12} = 3.76$, $p = 0.076$) nor the group × band interaction was significant ($F_{4,4} = 1.98$, $p = 0.159$). Nevertheless, detailed comparisons showed that rtACS strengthened long-range coherence in the alpha I ($t_{1,12} = 2.42$, $p = 0.032$) and alpha II bands ($t_{1,12} = 2.47$, $p = 0.029$).

Graphs analysis. Coherence results, converted into binary graphs, were further characterized with 2 graph measures: clustering coefficient and characteristic path length. Analysis of network clustering at baseline (figure 4) showed no group effect ($F_{1,26} = 0.78$, $p = 0.38$) and no group and band interaction ($F_{4,18} = 1.47$, $p = 0.21$). However, comparisons with t tests indicate that alpha II functional connectivity networks

Figure 3 Baseline and post-rtACS long-range functional connectivity

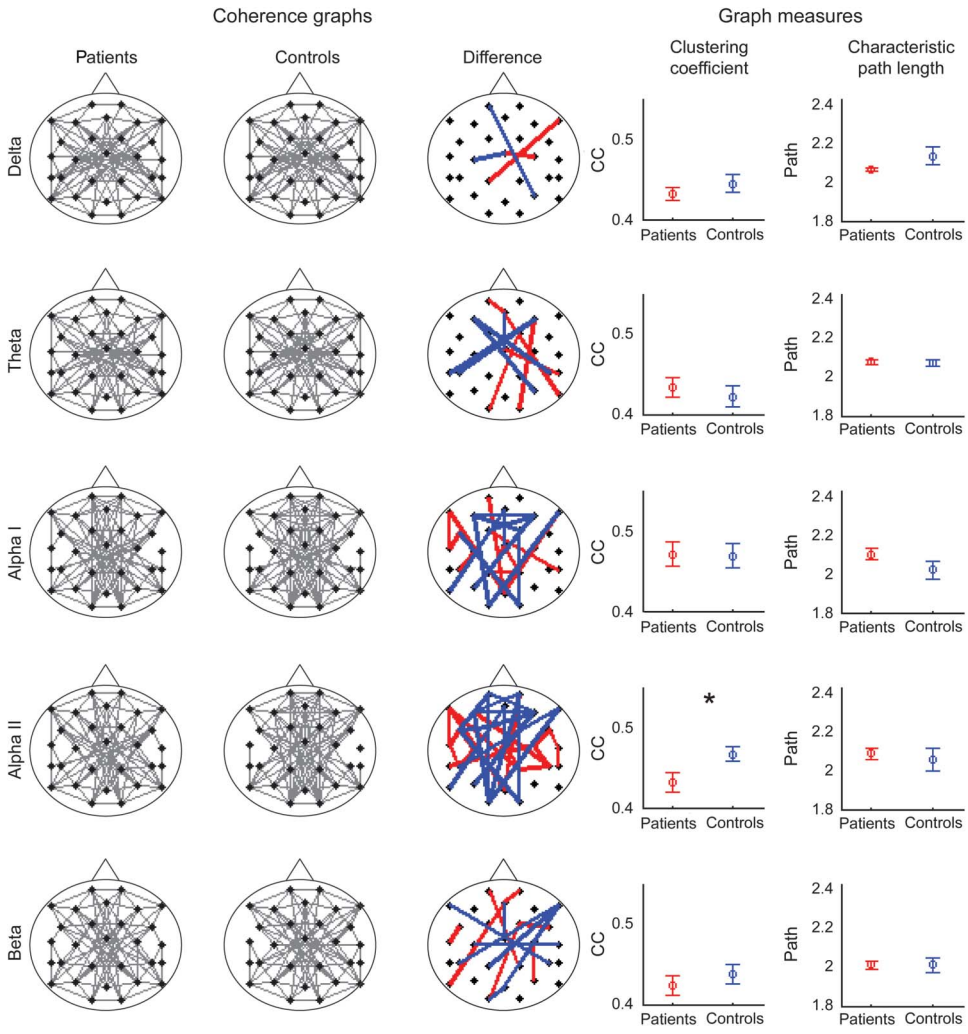


Long-range functional connectivity was defined as coherence or Granger causality (GC) between occipital and frontal areas of interest (between [O1, O2] and [FC1, FC2, Fz]). First, we found that at baseline, alpha II band long-range coherence was lower in patients than in control subjects. Second, using GC, we confirmed weaker long-range connectivity in patients. However, GC indicated between-group difference in the delta band. Third, rtACS strengthened long-range coherence in alpha I and alpha II bands, compensating for the deficit found at baseline. rtACS = repetitive transorbital alternating current stimulation.

of patients were less clustered than those of controls ($t_{1,26}$ = 2.13, p = 0.042). We did not find any between-group differences in characteristic path length.

rtACS was found to influence network clustering in stimulated patients. The group effect ($F_{1,12}$ = 3.84, p = 0.074; figure e-2) and the group × band interaction ($F_{4,4}$ = 2.51, p = 0.053) were not

Figure 4 Topology of coherence networks at baseline



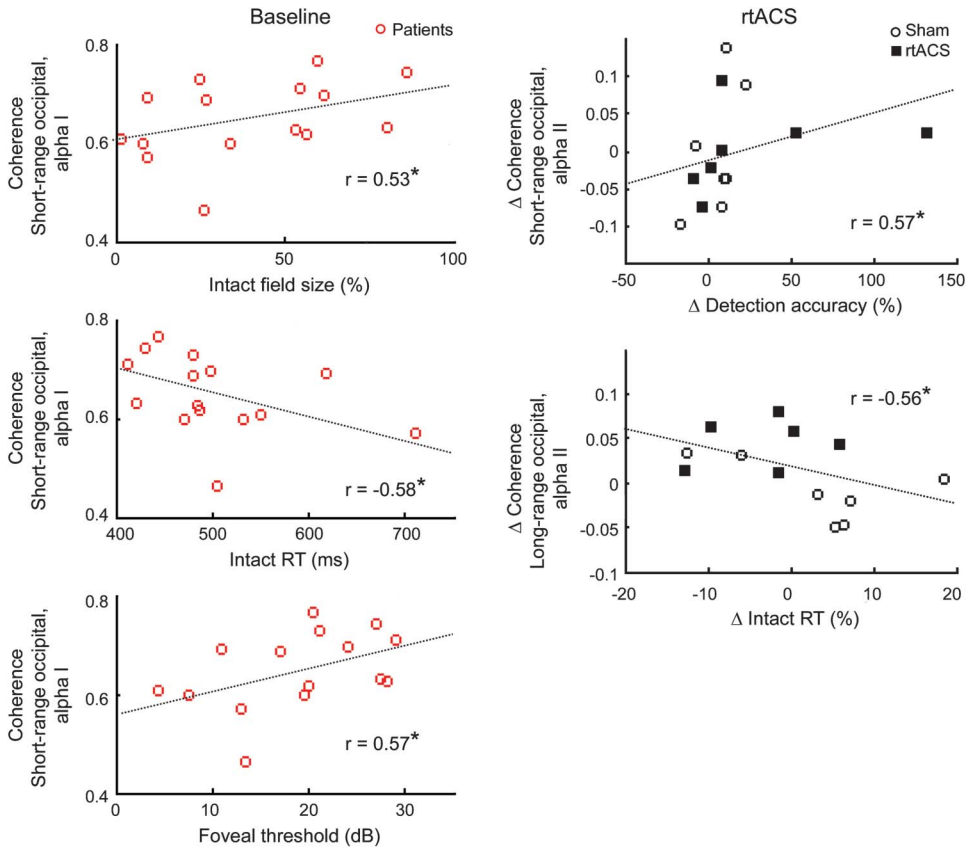
The first 3 columns show coherence network graphs with black dots representing standard EEG electrode positions, with frontal areas in the upper panel and occipital areas in the lower panel. All graphs contain the same number of edges (connections). The difference graphs (third column) display edges present in controls but missing in patients (blue) and edges missing in controls but present in patients (red). Close inspection reveals that the most pronounced between-group differences occur in the alpha II band, as graphs of patients show fewer edges between occipital and frontal nodes and in the frontal region, whereas they have more short-range connections in the central area. Difference in the network topology is confirmed by analysis of clustering coefficient (CC), indicating that the patients' networks are less densely clustered.

significant, but specific comparisons indicated increase of clustering coefficient in theta ($t_{1,12} = 3.72$, $p = 0.003$) and high-alpha bands ($t_{1,12} = 2.28$, $p = 0.041$). Concerning characteristic path length, we did not find an effect of group ($F_{1,12} = 1.46$, $p = 0.25$) or group × band interaction ($F_{4,4} = 1.25$, $p = 0.30$), but t test comparisons showed increases in alpha II band path length ($t_{1,12} = 2.56$, $p = 0.025$).

Functional significance of EEG measures. At baseline, higher local alpha I coherence at the occipital AOI was related to greater size of intact visual field as measured by HRP ($r = 0.53$, $p = 0.043$; figure 5), to faster processing speed as indicated by the intact field reaction time (RT) in HRP ($r = -0.58$, $p = 0.025$), and to better detection in the fovea as indicated by static perimetry threshold ($r = 0.57$, $p = 0.028$). Further, a post-rtACS increase in the local alpha II coherence at the occipital AOI was associated with increased detection accuracy in HRP ($r = 0.57$, $p = 0.035$), whereas an increase in long-range alpha II coherence was related to shorter intact field RT in HRP ($r = -0.56$, $p = 0.049$). Correlations between EEG measures and near/far acuity, kinetic perimetry, and NEI-VFQ results were not found.

DISCUSSION Our study revealed that patients partially blinded by optic nerve damage exhibit a breakdown of resting-state alpha band functional connectivity, and this loss of connectivity strength is related to visual perceptual capabilities. Specifically, in comparison to normally sighted controls, patients with prechiasmatic lesions had lower power of

Figure 5 Relationship between EEG and vision measures



At baseline, patients with stronger short-range alpha I coherence at the occipital region had bigger intact fields, as measured by high-resolution perimetry (HRP); shorter reaction time (RT) to HRP stimuli in the intact field; and better foveal detection in static perimetry. When analyzing change in EEG and vision measures, subjects with an increase in short-range alpha II coherence at occipital regions improved their detection abilities, and subjects with an increase in long-range alpha II coherence improved their processing speed in the intact field, as indicated by RT to perimetric stimuli. rtACS = repetitive transorbital alternating current stimulation.

oscillatory activity, decreased strength of short- and long-range functional connectivity, and less clustered patterns of the functional connectivity networks. Changes were found in a narrow frequency range, namely the high-alpha band (alpha II, 11–14 Hz). Further, a neuromodulation experiment with rtACS, previously shown to modulate alpha band activity,[9,10] was utilized to manipulate the network synchronization and study its impact on visual perception. rtACS strengthened alpha band functional connectivity, which was associated with perceptual improvements. This suggests that the alpha band oscillatory activity in the resting state (at eyes closed) is a marker of both loss and restoration of visual perceptual capabilities in partially blinded patients.

Little is known about the scope of brain network changes caused by visual system damage, especially its functional effects. Our results support the hypothesis that peripheral visual system damage leads to permanent alterations in spontaneous cortical activity. Of importance, we used resting-state EEG data recorded in a dark room with patients maintaining their eyes closed. Therefore, the between-group differences cannot be attributed to differences in visual input during the EEG recording. We rather interpret this as an indicator of permanent modifications of cortical networks by peripheral lesions. This is in line with the early concept of remote lesion effects as proposed by van Monakow in 1914 ("diaschisis")[15] and with recent fMRI studies in patients with glaucoma[16] and optic neuritis [17,18] (but see reference 19). In patients with prechiasmatic damage, changes in cortical activity are paralleled with structural alterations, namely a decrease of visual cortex gray matter density.[20] Remote effects of local, circumscribed lesions were also demonstrated in the motor system.[6–8] Although subjects tested in our study acquired lesions in adulthood, long after the critical period, the lesions still had an impact on cortical neurophysiology.

Specifically, we found that alpha band activity and alpha band connectivity are weaker in patients than in normally sighted controls and that connectivity strength is associated with the extent of vision loss. The finding that decreased spectral power of the alpha band is

related to lack of visual input is in line with previous studies showing decreased alpha activity in congenitally blind subjects.[21,22] How could this specific alpha band involvement be interpreted? Alpha activity is believed to perform inhibitory functions, so downregulation of alpha inhibition might be interpreted as a compensatory mechanism of the brain in response to reduced input, which would lead to increased sensitization of the deafferented regions. However, this hypothesis is at odds with the fact that stronger alpha band functional connectivity was related to better perceptual abilities of patients. Hence, alpha activity might play a facilitatory role in sensory and cognitive processes, e.g., reducing environmental or intrinsic noise.[23] Of interest, frontal brain regions modulate and control perception and attention by influencing occipital alpha rhythms.[24,25] Therefore, it is plausible that the disruption of fronto-occipital alpha band coherence in patients is a manifestation of impaired higher cognitive functions, e.g., attention. This can be tested by future studies.

Further, our results provide support for the concept that the 2 alpha sub-bands, low and high alpha, should be analyzed separately as they might serve different functional roles.[26] But what specific roles low and high alpha band play in visual perception remains to be studied. We recognize it might be reasonable to define frequency bands based on individual alpha frequency (IAF), but in our sample some patients did not have a clear alpha band peak in the spectral domain, making it impossible to define IAF. In fact, the very loss of the alpha peak in such patients further argues for alpha band activity being an important marker of visual perception.

We did not find signs of "compensatory" plasticity in patients, defined as greater oscillatory power or connectivity strength in patients compared to normally sighted subjects at baseline. Compensatory plasticity defined in this way was found in previous studies of subjects with prechiasmatic visual system damage[16–18] and it is a well-established phenomenon in congenitally blind subjects.[27–29] Further studies are now needed to elucidate whether and in what form the neurophysiologic markers of compensation occur.

Altered topology of connectivity networks was another marker of vision loss. Brain networks exhibit various spatial patterns of connections that can be assessed by graph measures.[14] The so-called small-world pattern, characterized by the existence of clusters of densely interconnected nodes and, at the same time, long-range connections between clusters, is hypothesized to be most optimal for information processing.[30] The deviation from the small-world pattern is a hallmark of many clinical conditions, including Alzheimer disease,[31] brain tumor,[32] and traumatic brain injury.[33] In the present study we show that the topology of functional connectivity networks is disrupted in patients with vision loss as well. Specifically, high-alpha band networks of patients were less densely clustered.

Of importance, in our study, functional connectivity was of relevance for perceptual abilities in patients. Therefore, we argue that not only local changes within and around the lesioned tissue—or the zone of primary deafferentation—determine the level of functional impairment, but also synchronization of the network (or lack thereof) might facilitate (or further hamper) perception in patients. Therefore, the disturbance of connectivity networks in patients might not only contribute to impaired vision at or near the zone of deafferentation but it might also comprise the mechanism behind "sight-blindness"[34]—the phenomenon of perceptual deficits occurring in the "intact" regions of the visual field not directly affected by tissue loss.[34–37]

Alpha oscillations can be entrained in healthy subjects[38] and in partially blind subjects[9,10] using alternating current stimulation. Therefore, in the second part of our study, we aimed to modulate alpha band functional connectivity and observe whether changes in connectivity strength covary with changes in vision measures. rtACS indeed increased alpha coherence and modified network topology in our patient sample, which is in line with previous studies on network effects of local brain stimulation.[39,40] Crucially, posttreatment strengthening of alpha band connectivity, with or without rtACS, was correlated with better perceptual functioning as shown by improved detection abilities and faster reaction times. This temporal covariation strengthens our argument concerning the role of the alpha band in visual perception. However, the rtACS experiment was not aimed at determining rtACS efficacy, which requires prospective clinical trials that are currently ongoing, but was instead used to check whether alterations of synchronizations would be correlated with perceptual improvements. More details on clinical studies showing rtACS efficacy are found elsewhere.[9,10]

The design of our study, involving comparisons at baseline (patients vs controls) and investigation of rtACS effects, allowed us to investigate the possible match of neurophysiologic deficits exhibited by patients and rtACS-induced effects. We show that some of the stimulation-induced changes were observed in the alpha II band (long-range coherence, network clustering) and in lower frequencies, e.g., theta and alpha I (power, short-range coherence). Of importance, it was the change in alpha II coherence that correlated with the clinical improvement. Further studies on noninvasive stimulation techniques in vision restoration are needed to achieve a better match between neurophysiologic deficits related to visual system damage (lack of alpha II) and neurophysiologic effects of noninvasive stimulation. Furthermore, the neurophysiologic effects should be further tested by employing high-density

EEG combined with source reconstruction methods in order to avoid possible confounds of volume conduction on functional connectivity estimates.

Permanent disturbance of the spontaneous cortical synchronization emphasizes that treating acquired blindness as only a consequence of local tissue loss is no longer sufficient. Patients might have deficits beyond simple visual field loss,[34–37] and visual dysfunctions in the "intact" visual field sectors should be taken into account as well when translating our observations to clinical diagnosis and neurorehabilitation. Furthermore, resynchronization of distributed networks is a possible mechanism whereby vision restoration can be achieved despite the local loss of visual system structures, as was shown in recent clinical trials.[9,10] The present study might therefore be able to guide the development of future therapeutic interventions for the blind by considering neural communication as represented by synchronization of large-scale neuronal networks.

AUTHOR CONTRIBUTIONS

Conceived and designed the study: C.G., B.A.S.; performed experiments: A.F.; analyzed the data: M.B., C.M.; supervised data analysis: H.H.; wrote the paper: M.B., B.A.S.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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