A (blue) light in the dark: Blue light modulates oscillatory alpha activity in the occipital cortex of totally visually blind individuals with intact non-visual photoreception

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Running head: Light modulates occipital alpha activity in blind

Abstract

The discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) marked a major shift in our understanding of how light is processed by the mammalian brain. These ipRGCs influence multiple functions not directly related to vision such as the synchronization of circadian rhythmicity, pupil constriction, the regulation of alertness and sleep, as well as the modulation of cognition. More recently, it was demonstrated that ipRGCs may also contribute to basic visual functions. The impact of ipRGCs on visual functions, independently of image forming photoreceptors, remains difficult to isolate, however, particularly in humans. We previously showed that exposure to intense monochromatic blue light (465nm) induced awareness of light in a forced choice task in three rare totally visually blind individuals without rod and cone function, but who retained non-visual responses to light, very likely via ipRGCs. The neural foundation of such light awareness in the absence of conscious vision is unknown, however. In this study, we characterized the brain activity of these three rare participants using electroencephalography (EEG), and demonstrate that unconsciously perceived blue light triggers an early and reliable desynchronization (i.e. decreased power) of the alpha EEG rhythm (8-14 Hz) over the occipital cortex. These results provide compelling insight into how ipRGC may contribute to transient changes in ongoing brain activity. They suggest that occipital alpha rhythm synchrony is modulated by non-visual ipRGCs photoreception; a process that may contribute to the awareness of light in those blind individuals.

Keywords: blindness, melanopsin, non-visual, blue light, circadian, alpha rhythm, ipRGC

Introduction

While vision is the best understood sensory system in the human brain, we are just beginning to understand the neuronal pathways mediating the 'non-visual' effects of ocular light exposure (Hubbard et al., 2013; Lucas et al., 2014). Evidence for non-rod, non-cone retinal photoreceptors had been suspected in human (Czeisler et al., 1995; Ruberg et al., 1996; Brainard et al., 2001a, 2001b; Thapan et al., 2001) before the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs) in mice (Provencio et al., 1998; Berson et al., 2002; Hattar et al., 2002). These retinal ganglion cells express the photosensory opsin melanopsin, which is maximally sensitive to short-wavelength blue light (~480nm). IpRGCs are the primary photoreception channel mediating non-visual functions of light including entrainment of the circadian clock, suppression of the pineal hormone melatonin, pupillary constriction, and acute enhancement of alertness and cognitive brain functions (Guler et al., 2008; Tsai et al., 2009; Lucas et al., 2014; Pilorz et al., 2016). Melanopsin-driven intrinsic responses of ipRGCs are more sluggish than the response of classical photoreceptor. IpRGCs also receive incoming signals from rods and cones, however, such that their response output is time-locked to the photic stimulation (Guler et al., 2008; Lucas et al., 2014). This photic response is then transferred to non-visual brain areas, including hypothalamic nuclei notably involved in circadian rhythmicity, and sleep-wake regulation (Milosavljevic et al., 2016; Jens Hannibal et al., 2017). IpRGC signals also reaches parts of brain primarily mediating vision, such as the lateral geniculate nucleus of the thalamus (Dacey et al., 2005; Jens Hannibal et al., 2017) and studies suggest that ipRGCs contribute to crude vision, brightness detection, and adjustment of rod and cones sensitivities (Ecker et al., 2010; Brown et al., 2012; Allen et al., 2014, 2017; Storchi et al., 2015; Mouland et al., 2017). Similarly to animal models, many human non-visual responses to light are more sensitive to shorter wavelength (blue) light exposures making them likely to be under ipRGC influence (Brainard et al., 2001a; Lockley et al., 2006; Chellappa et al., 2011; Santhi et al., 2012; Gaggioni et al., 2014). Isolating ipRGCs and melanopsin roles from those of rods, cones and other RGCs can be achieved in animals by knocking down, amplifying, or modifying part of the photoreception system (Davis et al., 2015; Procyk et al., 2015; Storchi et al., 2015; Allen et a., 2017). The exact role of ipRGCs remains difficult to isolate in humans, however, where specific genotypes perturbing the different parts of the retinal photoreception system are not available.

A rare and small group of totally visually blind human individuals -a dozen- have been reported to exhibit normal 24-hour circadian rhythms and have intact melatonin suppression, pupil constriction and/or circadian phase resetting in response to nighttime ocular light exposure (Czeisler et al., 1995; Klerman et al., 2002; Zaidi et al., 2007; Gooley et al., 2012). Critically, these light effects did not occur when these participants had their eyes covered. Neuro-ophthalmologic exam confirmed absence of rod and cone function in these individuals, strongly supporting that these rare individuals likely retain light perception via ipRGCs. This hypothesis is further supported by the observation that shorter wavelength light, in the blue range (~= 470 nm) was shown to be more efficient in triggering an alerting or pupil response in such individuals (Zaidi et al., 2007; Gooley et al., 2012). Furthermore, when exposed to blue light during a cognitively challenging task, these atypical blind individuals showed enhanced activation in a widespread subcortical and cortical network, including the occipital cortex (Vandewalle et al., 2013). Altogether, these results support the notion that these rare blind individuals provide a unique human model to study the role of ipRGCs in the absence of conscious vision.

At the frontier between vision and non-vision, these rare patients present the ability to non-randomly guess the presence or absence of light in a two-alternative choice forced task (2AFC) indicating some sort of awareness for light in the absence of conscious vision [n = 1 (Zaidi et al., 2007); n = 3 (Vandewalle et al., 2013)]. The brain mechanisms of such awareness of light are unknown. Cortical oscillations in the alpha range (8-14 Hz) may provide important insight to address this issue. Exposure to blue light at night modulates high alpha power in sighted individuals (~10-12Hz) (Lockley et al., 2006; Münch et al., 2011; Rahman et al., 2014), and in a blind individual with presumably intact ipRGCs (~8-10 Hz) (Zaidi et al., 2007). These changes in alpha power are typically reported over prolonged exposure to light and seem to take minutes to tens of minutes to be detected. They have not been investigated, however, at shorter time scales using exposure to light lasting only of seconds. Alpha oscillations in sighted individuals show transient responses to visual stimulation, which emerges in the order of milliseconds to seconds. These are thought to reflect changes in visual attention allocation and are typically observed as a transient decrease in alpha power, or a transient desynchronization, over the area of the brain that processes the stimulus presented (Pfurtscheller and Lopes da Silva, 1999; Klimesch et al., 2007; Jensen and Mazaheri, 2010;

Bollimunta et al., 2011; Foxe and Snyder, 2011). Interestingly, recent evidence suggests that these more transient oscillatory changes could be modulated by prior exposure to bright blue light, likely implicating ipRGCs (Min et al., 2013; Newman et al., 2016). However, the transient response to light has not been investigated in blind participants retaining non-visual responses. We hypothesize that exposure to light will transiently decrease alpha power over the occipital cortex during exposure in these rare blind individuals supporting that light awareness arises from a specific impact on visual attention.

To test this hypothesis, we analyzed the EEG recordings acquired while three totally visually blind individuals with intact non-visual responses to light participated during a forced choice task for which they choose the presence or absence of light non-randomly despite their complete lack of conscious vision (Vandewalle et al., 2013). Spectral analysis and EEG source reconstruction computations were performed to quantify short-term (10s) light-induced changes in alpha rhythm over the occipital cortex task.

Materials and Methods

Except for electrophysiological data analyses, methods included here were described previously (Vandewalle et al., 2013).

Participants

Participants were three totally visually blind individuals [1 female, range 60-67 years; see Supplementary table S1 for detailed characteristics, previously reported in (Vandewalle et al., 2013)]. Although none of the participants reported any conscious awareness of light, an intact melatonin suppression responses to white or blue light was demonstrated in all three participants in previous studies (Klerman et al., 2002; Zaidi et al., 2007). Participant 1 had pupil muscle damage during lens removal surgery for cataract problems and did not respond to a standard pen-light examination. Participant 2 exhibited pupil constriction if the pen-light exposure was continued for more than a few seconds (Gooley et al., 2012). Participant 3 had no clearly distinguishable pupil. In previous visits to Boston, a fundoscopic examination in Participants 1 and 2 confirmed atrophy of the retinal pigment epithelium, with thinning of retinal vessels

and bone spicule pigmentation. These findings were confirmed on several occasions by different ophthalmologists who examined the patients independently.

Experimental design

The experiment was conducted in an electromagnetically shielded and sound attenuated room in complete darkness. Visual stimulation was elicited via an array of 48 blue light emitting diodes [LED, peak = 465nm, Full Width at Half Maximum (FWHM) = 27nm] behind a 21x11 cm diffusion glass with ultraviolet and infrared filters. Photon flux at corneal level was 9.7×10^{14} photons/cm^2/sec. Brief blue-light flashes were administered during four blocks of 200 trials (duration=500ms, ISI=1600-1800ms), totaling 800 trials, to record potential visually evoked potential (VEP). EEG recordings were also acquired during a two-alternative forced choice task (2AFC). Each trial lasted 20s during which blue light was pseudo-randomly presented during the first or last 10s (10s light ON and OFF). The halfway point of the trial was signaled by a brief auditory pure tone (500ms, 1000Hz). After each trial, the participant was asked whether the photic stimulation occurred during the first or second half of the trial. Participants were presented with 40 trials in total resulting in 80 segments, half with and half without blue light stimulation. Due to a scripting error, only the overall performance on the task is available, i.e., responses to individual trails were not recorded, precluding any correlational analyses between EEG and behavioral measures at the individual trial level. In addition, datasets were acquired for 10s trials (5s light ON and OFF; 2 participants since data from one participants could not be used) and 4s trials (2s light ON and OFF; 3 participants), and processed in the same way. Results of a standard VEP analysis as well as performance on the 2AFC task were reported previously (Vandewalle et al., 2013; see also supplementary Figure S1). The spectral analyses of 2AFC EEG data described below were not previously reported.

EEG data acquisition and preprocessing

EEG was recorded continuously from 40 Ag-AgCl electrodes on an extended 10-20 system (Neurosoft Inc., Sterling, VA), using a sampling rate of 1000Hz. The signal was filtered online using a band-pass filter (0.1-100Hz), and referenced to the algebraic average of the two mastoids. Impedances were kept below 5 kΩ. The signal was filtered offline with a low-pass filter with a cut-off at 30Hz, re-referenced to the algebraic

average across electrodes, and downsampled to 150Hz. For VEP data, artifacts resulting from eye blinks, muscle tension, and electronic noise were removed following visual inspection. Event-related potentials were computed by averaging all trials, subtracting a baseline of 150ms before the onset of photic stimulus. For the 2AFC task due to the long duration and limited number of trials, extended infomax independent component analysis (ICA) was performed with a weight change stop criterion of 10^{-7}. Components reflecting ocular artifacts (e.g. eye blinks and lateral saccades) were rejected based on visual inspection of topography and time course.

Spectral analysis

All offline analysis was conducted using Fieldtrip (Oostenveld et al., 2011), under Matlab (The Mathworks Inc, Natick, MA). Analysis of the data from the 2AFC task was performed separately for the 10s exposure to light (Light ON), and darkness (light OFF). Spectral analysis was applied over the entire 10s period for frequencies between 5 and 25Hz, using the multitaper method (Mitra and Pesaran, 1999) with 19 Slepian tapers, resulting in a frequency smoothing of ±1Hz. The same analysis was performed for the other two stimulation durations.

Statistical analysis was performed on the log-transformed power spectra, and centered on the alpha band (8-14Hz) in occipital electrodes (O1, Oz, and O2). Between-trial comparisons for the light-ON *versus* light-OFF segments were conducted for each individual participant using independent sample t-tests. A cluster permutation approach was used (500 permutations) to control for multiple comparisons using a maximum cluster extent threshold (Maris and Oostenveld, 2007). Permutation tests provide a robust inferential statistic, without assumptions about the shape of the sampling distribution. Furthermore, by selecting a liberal alpha-range (8-14Hz), the method optimally captures potential variation in the individual alpha peak frequency.

To investigate the time-course of alpha power modulation in response to blue light further, time-frequency analysis was performed using 6 cycle Morlet wavelets (100ms steps, 1Hz frequency resolution). Here, the frequency-averaged alpha power time course was compared between the light-ON versus light-

OFF condition and clustering was performed across time (0-10s post stimulus onset) and space (electrodes).

Source-level analysis

In line with the recommendations by Gross et al. (Gross et al., 2012), statistical analysis of the differences between the light-ON and light-OFF condition were performed at the sensor level, and subsequent source reconstruction was performed to identify the generators.

Source reconstruction was performed using structural MR-images from each of the three blind participants. T1 weighted images (voxel size: 1x1x1mm, TR=2.3s, TE=2.91ms, flip angle=9°, field of view 265x224mm) were acquired on a 3-T TIM-TRIO MR scanner (Siemens, Erlangen, Germany). Individual T1 MRI images were segmented in cerebrospinal, white matter, grey matter and skull compartments. The white and grey matter brain compartments were used to construct individual head models using the Boundary Element Method (BEM) (Oostenveld et al., 2003). Source activity was projected on a regular three dimensional grid (10x10x10mm), using a frequency domain beamformer, called Dynamic Imaging of Coherent Sources (Gross et al., 2001; Liljeström et al., 2005). A regularization of 15% was applied. To identify robust peak differences in the alpha range, statistical maps for the difference between the light-ON versus light-OFF conditions were computed using independent-sample t-tests, using a permutation approach, with a threshold of $\alpha = 0.05$.

Results

Behavioral results

As reported previously (Vandewalle et al., 2013), for the 10 seconds light exposure, both participant 1 and 2 showed a very high accuracy in guessing when the blue light was presented (95%, and 80%, both $p<.001$). Participant 3 also showed performance rates different from chance although accuracy was inverted (30%, $p=.008$). Participants 1 and 2 (95%, and 65%, $p<.001$, and $p=.04$), but not participant 3 (62.5%, $p=.08$) showed above-chance performance for the 5 second exposure to blue light. During the 2

second stimulation period, only participant 1 (95%, $p<.001$) maintained accurate performance rates, while both participant 2 and 3 responded at chance (both $p>.4$).

Visual Evoked potentials

Also as previously reported (Vandewalle et al., 2013), there was no evidence for visual evoked activity elicited by the average across ~800 trials of brief photic stimulation with blue light in any of the three participants (Fig. S1).

Light induced modulation of alpha power during 2AFC task

Spectral analysis of the alpha power difference between the light-ON *versus* light-OFF across occipital electrodes and over the entire 10s time windows revealed significantly reduced alpha power in all three participants (participant 1: $p=.034$; participant 2: $p=.024$; participant 3: $p=.028$) (Fig. 1A). The difference between conditions was strongest in the upper alpha range [11-14Hz] for each of the three participants (participant 1: 12.1-12.8Hz; participant 2: 12.8-13.9Hz; participant 3: 11.3-12.5Hz) The same analysis for the 2s and 5s intervals did not yield significant difference between Light ON and Light OFF periods (Fig. S2).

Subsequent source reconstruction was performed (i.e. not restricting to occipital electrodes) on the entire 10s time window, using the individual peak in alpha power difference between light-ON and light-OFF (participant 1: 12.2 Hz; participant 2: 13.4 Hz; and participant 3: 11.3Hz; see highlighted peaks on Fig. 1A). Although the analyses were not restricted to the posterior part of the brain, the neural generators of the alpha power decrease during light-ON was localized primarily to occipital cortex in participants 1 and 2, and to occipito-parietal cortex in participant 3 (Fig. 1B). In addition, a distinct conjunction analysis, seeking for significant sources common to all participants combining all three statistical maps, revealed an area in bilateral superior occipital gyrus (SOG) (Fig 2). The light-induced decrease in alpha power observed over occipital sensors seems therefore to be mostly confined to the occipital cortical areas.

Finally, Figure 1C shows the time-frequency maps for the statistical difference between the light-ON and light-OFF condition for each of the three participants. Exploratory follow-up analyses on the upper alpha range (11-14Hz) performed across time and space revealed that differences between conditions were driven by a transient alpha suppression effect. While participant 1 showed a broadband desynchronization

shortly following stimulation onset (400-600ms, *p*=.01), however, participant 2 (6200-6400ms, *p*=.012) and 3 (6400-6600ms, *p*=.038) showed stronger desynchronization only after several seconds. Interestingly, these latencies partly mirrored the behavioral responses. Only participant 1 showed accurate performance in detecting the blue light during the 2s stimulation period, while all participants showed non-random behavior at 5 and 10 seconds.

Discussion

IpRGCs participate in multiple physiological regulatory mechanisms. Isolating their contribution is a challenge, however. First, melanopsin spectral sensitivity overlaps with those of rods and cones while the light level required to elicit a melanopsin driven response is somewhere in between rod saturation level and cone threshold sensitivity (Lucas et al., 2014). In addition, although ipRGCs are the main (if not the only) channel to transmit photic information to impact non-visual functions, ipRGCs receive input from rods and cones that add to their intrinsic melanopsin driven response to set overall ipRGCs output (Lucas et al., 2014). In addition, rods can contribute to non-visual responses at light intensities which would be considered completely saturating and unable to contribute to image formation (Keenan et al., 2016). Finally, in addition to their central non-visual role, ipRGCs contribute to basic visual function. They contribute to crude visual discrimination and set light adaptation of classical photoreceptors (Ecker et al., 2010; Brown et al., 2012; Allen et al., 2014, 2017; Mouland et al., 2017). Sophisticated animal models can be built to knock down, amplify, or modify part of the photoreception system and dissect out ipRGCs and melanopsin roles from those of rods, cones and other RGCs. In humans, such models cannot be built such that, even though ipRGCs are more than likely to participate to non-visual responses to light, their contribution is difficult to confirm. The rare totally blind individuals with undetectable rod and cone functions, but with intact non-visual responses to light and presumably intact ipRGCs, provide therefore a unique human model to investigate the impact of light in the absence of conscious vision and very likely through melanopsin-driven intrinsic photosentivity of ipRGC (Czeisler et al., 1995; Klerman et al., 2002; Zaidi et al., 2007; Gooley et al., 2012; Vandewalle et al., 2013).

In this study, we recorded electroencephalographic (EEG) responses to brief exposure to intense monochromatic blue light (465nm) in three of these rare cases. As already reported (Vandewalle et al., 2013), they have non-conscious vision; ophthalmologic examination find no evidence for remaining rod and cone function and we confirm that they did not respond to 500ms light flashes in extended VEP procedure (800 trials). Yet, they are able to guess successfully on the presence or absence of light in a forced choice task, particularly if light pulses last 10s and less evidently for 5s or 2s exposure (Vandewalle et al., 2013). Our novel analyses presented here show that 10s of light exposure is able to reliably induce a decrease of alpha power in the three participants tested. Although the exact frequency seems to slightly vary across individuals (peak of alpha power decrease between 11.3Hz and 13.4 Hz), this decrease is more prominent in the higher alpha band between 11 and 14Hz rather than low alpha. These results suggest that ipRGCs in humans may regulate cortical synchrony in higher alpha frequency band within seconds in humans and that this influence may participate in the concomitant awareness for light during the forced choice task.

Alpha oscillations are thought to reflect a sensory gating, or prioritization, mechanism (Klimesch et al., 2007; Jensen and Mazaheri, 2010). For example, fluctuations in the cortical alpha rhythm have been associated with visual-spatial, sensory, and object-based attention (Jokisch and Jensen, 2007; Foxe and Snyder, 2011; Haegens et al., 2011; Frey et al., 2014), including response to blue-enriched white light (Newman et al., 2016). Specifically, transient reduced alpha power typically reflects enhanced neuronal activity, or excitability (Romei et al., 2008; Romei, Gross, & Thut, 2010; Romei, Rihs, Brodbeck, & Thut, 2008), while transient enhanced alpha power is considered a marker for cortical inhibition (Klimesch et al., 2007; Jensen and Mazaheri, 2010). For example, if alpha power in a given sensory area is low, participants are more likely to perceive a near-threshold event in the same modality (Linkenkaer-Hansen et al., 2004; Romei et al., 2010; Weisz et al., 2014).

If transient reduced alpha power is a marker for increased cortical excitability in visual areas, or indeed a precursor to visual awareness, this could explain why participants made non-random selections about the presence or absence of the blue light during the 2AFC task. The moment at which desynchronization is strongest varied from ~500ms in participant 1 to ~6s in the other two participants, which is long, in any case, with respect to classical rod-cone photoreception. This relatively late onset

response may be related to the relatively sluggish responses of the intrinsic melanopsin-driven light sensitivity of ipRGC in the absence of classical photoreceptor inputs (Berson et al., 2002; Dacey et al., 2005; Lucas et al., 2014), explaining the absence of observable effect after short and rapid visual stimulation like in our VEP testing (see SFigure 1). An interesting additional observation regarding the sample in the current study is that the time duration of the stimulation at which individual participants show non-random responses mirrors the latencies at which desynchronization is strongest (i.e., directly post-stimulus onset or after several seconds). Participant 1, however, who demonstrated early desynchronization in the 10s trials, and accurate light detection for all trial types (i.e. 2, 5 and 10s), showed no significant spectral changes for the 2s trials (EEG data for the 5s segment could not be used). Even if there was a trend in the expected direction also for the 2s segment of participant 1, it was not significant. The reasons for such discrepancies are unclear. The spectral resolution is of course reduced if we take shorter time windows for the spectral analysis. Also, the data of the 2s period for participant 1 has a much stronger variance than the 10s period which may impair statistics. While these findings are not direct evidence for a relationship between non-conscious responses to blue light, ipRGCs and alpha power modulation, it is certainly an interesting avenue for further investigation.

It is well-known that exposure to light enhances alertness and attention. The changes are evident through a decrease in delta (0.5-4Hz) and theta (4-8 Hz) power in EEG recordings of spontaneous (i.e. task free) brain activity (Cajochen et al., 2000; Rahman et al., 2014). Both theta and delta are established markers of sleep need and sleepiness, respectively, during sleep and wakefulness (Cajochen et al., 2002). An increase in alpha power also accompanies exposure to blue light at night (Lockley et al., 2006). Whether such an increase takes place within the first seconds of light exposure is not known. Our data suggest that it is the case, at least in blind individuals with intact non-visual photoreception, while performing a task, as we detect a decrease in alpha power during 10s exposure to intense blue light. This decrease in alpha power during task performance is therefore likely to represent a distinct feature of the impact of light on sensory activity that would be unrelated to the longer term (minutes or tens of minutes following light exposure) and widespread (not sensory-specific) increase in alpha power and alertness induced by light found in spontaneous EEG recordings (Romei et al, 2008; Jensen et al., 2010). How related these two

phenomena are during spontaneously responses or during a task at what seems to be different time scales requires further investigation.

We previously reported in sighted participants that blue light can induce a non-visual modulation of cognitive brain activity while performing auditory cognitive tasks (involving working memory, attention, emotion processing) that could be detected in brain areas involved in the ongoing task, including in the occipital cortex (Vandewalle et al., 2006; Daneault et al., 2014). When investigating the impact of intense blue light exposure in the three blind individuals with intact non-visual responses to light included in this paper, we observed a large increase in brain responses to an auditory working memory task over the occipital cortex (Vandewalle et al., 2013). This light-induced occipital recruitment may arise from the documented crossmodal reorganization of the occipital cortex of blind people (Collignon et al., 2009; Dormal et al., 2012), including the processing of auditory (Collignon et al., 2011b) and higher-level cognitive task like memory (Amedi et al., 2003). In other words, blue light exposure in those blind people could indirectly boost task-related activity (e.g. auditory working memory) rooted in the occipital cortex of blind people. We instead favor the hypothesis that the light-induced alpha desynchronization observed in our sample of blind individuals is due to residual effect of ipRGC onto occipital regions. The transient reduction in alpha we observe in our study is mainly confined to the occipital cortex and is observed in the absence of a concomitant auditory or higher-level task. Melanopsin ipRGCs, which are presumably intact in our sample, have been reported to project to the lateral geniculate nucleus and contribute to crude detection of visual features (Dacey et al., 2005; Ecker et al., 2010; Brown et al., 2012; Allen et al., 2014; Jens Hannibal et al., 2017).

In summary, we demonstrate that even short exposure to short-wavelength blue light, in the order of several seconds, reduces alpha power in occipital cortex relative to a period of darkness in a rare population of totally visually blind participants lacking image forming photoreceptors (rods and cones) but with presumably intact ipRGC-mediated light response. The fact that oscillatory changes in the current study seem to be largely confined to occipital areas, as well as the observation that participants demonstrate non-conscious behavioral sensitivity to the presence of blue light could have profound consequences for cortical reorganization of occipital cortex in blind participants with intact ipRGCs. Specifically, the presence of

residual pathways still attuned to ipRGCs influence in the occipital cortex of blind people could prevent the full reorganization of those regions toward non-visual functions typically observed in totally blind people (Collignon et al., 2013), and therefore might weight in the decision to attempt sight restoration in this population (Collignon et al., 2011a; Heimler et al., 2014).

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Figures

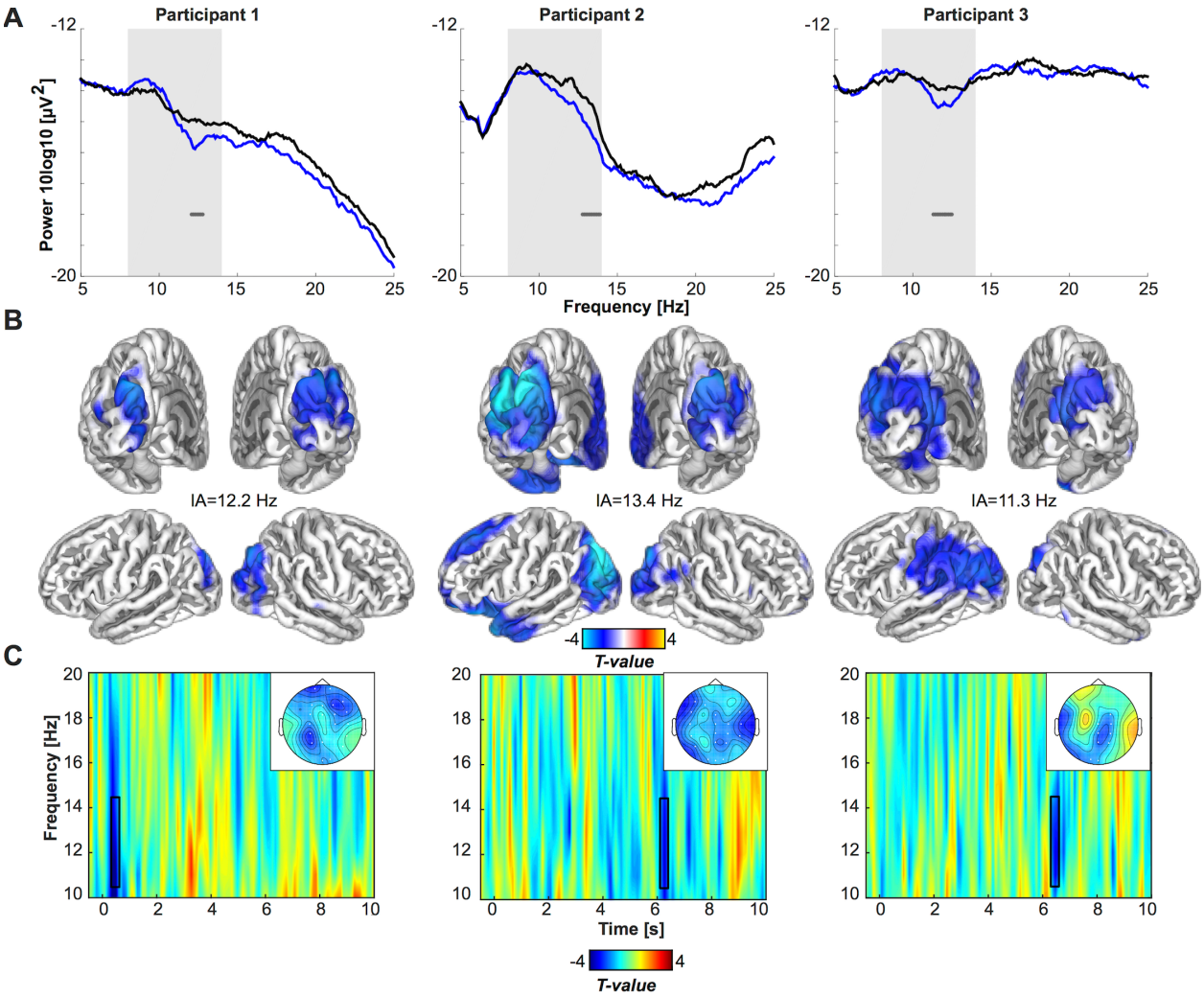


Figure 1. Desynchronization of the occipital alpha/low beta rhythm during a 10 second of stimulation with blue light in three blind participants with intact non-visual photoreception. **(A).** Frequency spectra for the entire 10s period of blue light (blue), and darkness (black) show differences between conditions in all three participants (horizontal gray bar, p<.05, cluster-corrected) for the frequency band of interest (shaded area, 8-14Hz). **(B).** Source reconstructions depict the difference between conditions (thresholded at p<.05), at the individual alpha frequency showing greatest light-induced decrease (see main text). Statistical maps (t-values) of the topographies with the absolute difference between conditions at the individual alpha frequencies show that the spatial extent of the decrease in alpha power is largely restricted to occipital electrodes. **(C)** Time-frequency representations illustrate differences between the light-ON versus light-OFF condition in time. Open rectangles highlight the time range of greatest difference (*p*<.05, cluster-corrected)

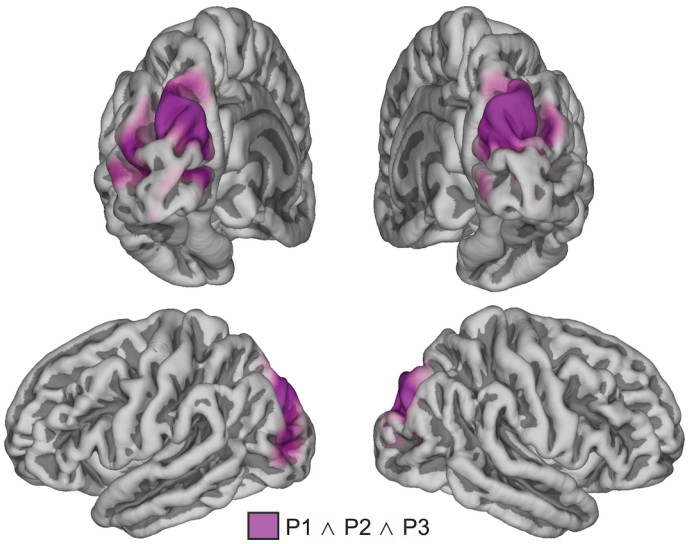
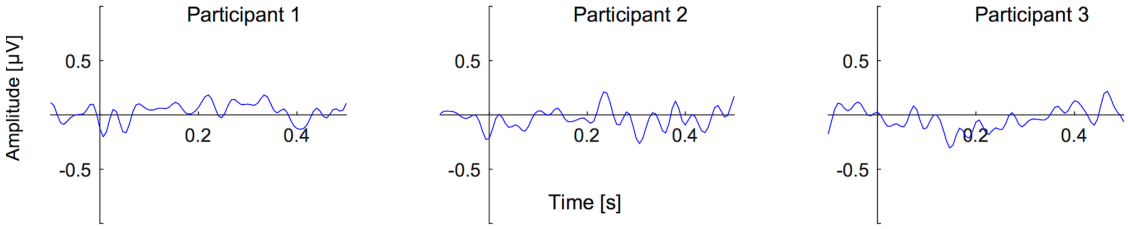
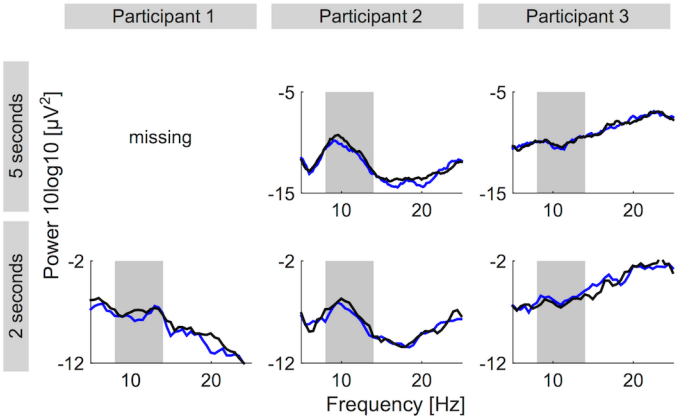


Figure 2. Conjunction analysis across the source statistical maps identified an area in bilateral superior occipital gyrus and cuneus as a significant ($p<.05$) cortical source of the alpha suppression in response to blue light common to all three participants.

Supplementary materials



Supplementary Figure 1. Trial averages in the time domain for brief photic stimulation with blue light, relative to baseline showing a marked absence of visual evoked potentials (VEP; 800 trials).



Supplementary Figure 2. Frequency spectra for the light on (blue) versus light off (black) conditions for the three participants (columns), and the two shorter stimulation periods than the 10s period presented in the main manuscript (from top to bottom: 5s, 2s), averaged across occipital electrodes.

SUPPLMENTARY TABLE 1: Participants characteristics

		Participant 1	**Participant 2**	**Participant 3**
Age		67	60	66
Sex		Female	Male	Male
Body Mass index (BMI)		27.3	30.0	27.4
Cause of blindness		Retinitis Pigmentosa	Retinitis Pigmentosa	Retinopathy of Prematurity
Years of total blindness		10	25	66
Chronotype (Horne & Ostberg, 1976)		62 - Moderate morning type	72 - Moderate morning type	68 - Moderate morning type
Anxiety (from 0 = lowest, to 63 = highest) (Beck et al., 1988)		5	0	2
Mood (from 0 = best, to 63 = worst) (Steer et al., 1997)		0	0	0
Sleep disturbances (from 0 = lowest, to 21 = highest) (Buysse et al., 1989)		3	10	4
Daytime propensity to fall asleep (Johns, 1991)		1	4	16
Laterality		Right handed	Right handed	Right handed
Time zone difference with Montreal		-1h	0h	-3h
Cigarette consumption		No	No	No

Medication		None	None	Low dose of blood pressure medication
Years of education		17	12	12
Alcohol consumption (units/week)		<1	<1	0
Caffeine consumption (cups/day)		2	5	2
Last confirmation of light – induced melatonin suppression		Yes, in 2008	Yes, in 2006	Yes, in 2002
Previous standard ERG examination (no detectable signal)		No	No	Yes, in 1994
Previous standard VEP examination (no detectable signal)		Yes, in 2008	Yes, in 2006	No
Pupil response to prolonged light exposure (> 5s)		No	Yes	No
Participated in a published study		No	Yes (Zaidi et al., 2007)	Yes (Klerman et al., 2002)

CHRONOTYPE was assessed by the Horne-Östberg Questionnaire (Horne & Ostberg, 1976); *ANXIETY LEVEL* was measured on the 21 item Beck Anxiety Inventory (Beck et al., 1988); *MOOD* was assessed using the 21 item Beck Depression Inventory II (Steer et al., 1997); *SLEEP DISTURBANCE* was determined by the Pittsburgh Sleep Quality Index Questionnaire (Buysse et al., 1989); *DAYTIME PROPENSITY TO FALL ASLEEP* during daytime non-stimulating situations was assessed by the Epworth Sleepiness Scale (Johns, 1991). *ERG*: electroretinogram; *VEP*: visually evoked EEG potential.

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