Published in final edited form as:

Eur J Neurosci. 2015 April ; 41(7): 923–937. doi:10.1111/ejn.12849.

Spatio-temporal dynamics of adaptation in the human visual system: A high-density electrical mapping study

Gizely N. Andrade^{1,2}, John S. Butler^{1,3,4}, Manuel R. Mercier¹, Sophie Molholm^{1,2}, and John J. Foxe^{1,2,3,4}

¹The Sheryl and Daniel R. Tishman Cognitive Neurophysiology Laboratory, Children's Evaluation and Rehabilitation Center (CERC), Departments of Pediatrics and Neuroscience, Albert Einstein College of Medicine, Van Etten Building – Wing 1C, 1225 Morris Park Avenue, Bronx, NY 10461, USA ²The Graduate Center of the City University of New York, Departments of Psychology & Biology, 365 5th Avenue, New York, NY 10016, USA ³Trinity Centre for Bioengineering, Trinity College, Dublin 2, Ireland ⁴Trinity College Institute of Neuroscience, Trinity College, Dublin 2, Ireland

Abstract

When sensory inputs are presented serially, response amplitudes to stimulus repetitions generally decrease as a function of presentation rate, diminishing rapidly as inter-stimulus-intervals (ISIs) fall below a second. This “adaptation” is believed to represent mechanisms by which sensory systems reduce responsivity to consistent environmental inputs, freeing resources to respond to potentially more relevant inputs. While auditory adaptation functions have been relatively well-characterized, considerably less is known about visual adaptation in humans. Here, high-density visual evoked potentials (VEPs) were recorded while two paradigms were used to interrogate visual adaptation. The first presented stimulus pairs with varying ISIs, comparing VEP amplitude to the second stimulus to that of the first (paired-presentation). The second involved blocks of stimulation (N=100) at various ISIs and comparison of VEP amplitude between blocks of differing ISIs (block-presentation). Robust VEP modulations were evident as a function of presentation rate in the block-paradigm with strongest modulations in the 130–150ms and 160–180ms visual processing phases. In paired-presentations, with ISIs of just 200–300 ms, an enhancement of VEP was evident when comparing S2 to S1, with no significant effect of presentation rate. Importantly, in block-presentations, adaptation effects were statistically robust at the individual participant level. These data suggest that a more taxing block-presentation paradigm is better suited to engage visual adaptation mechanisms than a paired-presentation design. The increased sensitivity of the visual processing metric obtained in the block-paradigm has implications for the examination of visual processing deficits in clinical populations.

Correspondence: john.fox@einstein.yu.edu.

Conflict of Interest Statement

All authors of this paper declare no conflicts-of-interest, financial or otherwise, that could have biased their contributions to this work. The senior author, Dr. Foxe, attests that all authors had access to the full dataset and to all stages of the analyses.

Keywords

Vision; VEP; Visual Gating; inhibition; habituation; EEG; plasticity; ERP

INTRODUCTION

Adaptation of neural responses to invariant or repetitive environmental inputs is a fundamental property of sensory processing, believed to represent a mechanism by which sensory systems attenuate representational redundancy (Fang, Murray et al. 2005; Fiebelkorn, Foxe et al. 2011; Cattani, Bachatene et al. 2014). Adaptation typically manifests as a rapid attenuation of neural responsiveness, providing a good metric of short-term neural plasticity. The hypothesized reduction in representational redundancy likely serves to enhance the brain's ability to detect more relevant novel environmental changes. Visual adaptation can be examined by comparing changes in the amplitude of the visual evoked potential (VEP) to repetition at varying presentation rates. Terminology in the field is not always consistent, with such VEP adaptation effects sometimes referred to as “habituation” or “sensory gating”. Adaptation to presentation rates can be calculated across pairs of consecutive trials by comparing VEP amplitudes between the first and second stimulus of a pair (Adler 1985). Alternatively, comparisons can be made between VEPs elicited by trains of stimuli presented at fixed rates, where rate is varied across blocks of trials (Megela and Teyler 1979).

In humans, adaptation to repetitive auditory stimulation has been extensively studied and is now quite well characterized (Fruhstorfer, Soveri et al. 1970; Potter, Summerfelt et al. 2006; Rosburg, Zimmerer et al. 2010; Chang, Arfken et al. 2011; Grzeschik, Bockmann-Barthel et al. 2013; Lanting, Briley et al. 2013). A main finding in both auditory habituation and gating studies has been that the shorter the period between stimulus presentations, the greater the attenuation observed (Roth, Krainz et al. 1976; Budd, Barry et al. 1998; Muller-Gass, Marcoux et al. 2008; Rosburg, Zimmerer et al. 2010; Pereira, Cardoso et al. 2014). Although the mechanisms behind auditory adaptation are not fully understood, several studies implicate local mechanisms such as neuronal refractoriness and pre-synaptic calcium influx, particularly in paired-presentation designs. Also implicated are top-down mechanisms related to expectancy, sensory memory, and novelty detection, particularly when more than 2 stimuli are used, such as in a block design. These plasticity mechanisms are thought to involve NMDA-mediated glutamate transmission, GABA-ergic inhibition, and changes in the ongoing oscillatory activity of the brain (e.g. in the gamma band frequency) (Zucker 1989; Chung, Li et al. 2002; Friston 2005; Grill-Spector, Henson et al. 2006; Brockhaus-Dumke, Mueller et al. 2008; Orekhova, Stroganova et al. 2008; Carlen, Meletis et al. 2012). In contrast, studies of adaptation to visual stimulation are relatively sparse and have yielded inconsistent and even contradictory findings.

Here, we set out to comprehensively map adaptation functions of the visual system in healthy adults using high-density electrical mapping techniques. Most of the previous literature has been limited to low-density montages and there has been a strong tendency to focus on amplitude changes at discrete VEP components, providing a somewhat static view

of what is undoubtedly a dynamic ongoing process. This, along with a bias towards paired-presentation paradigms and a lack of studies examining VEP adaptation to simple presentation rate manipulations has provided an incomplete picture of visual adaptation processes.

In the auditory and somatosensory systems, the amplitude of the neural response dramatically attenuates following repeated rapid paired-stimulation (McLaughlin and Kelly 1993; Hetrick, Sandman et al. 1996; Arnfred, Eder et al. 2001; Braff, Light et al. 2007), although it should be noted that the auditory evoked potential (AEP) can also increase in response to the second stimulus in a pair when very short inter-stimulus-intervals (ISIs) are employed (Loveless, Hari et al. 1989; Loveless, Levanen et al. 1996). In vision, findings are considerably less clear-cut. For example, there are reports of strong adaptation to paired-stimuli using monocular stimulation (Wastell and Kleinman 1980), while others report weakened adaptation to binocularly presented paired-stimuli as compared to other sensory modalities (Davis, Osterhammel et al. 1972), and yet others report adaptation effects to paired-stimuli that are specific to right lateral occipital scalp-sites (Gjini, Sundaresan et al. 2008). On the other hand, there are also reports of adaptation effects over bilateral occipital scalp to non-identical, spatially segregated stimuli (Gawne, Osbourne et al. 2011). Given the differences in the experimental paradigms used to assess visual adaptation to paired-stimuli, it is difficult to form a coherent picture of which effects are consistent, and what variables are driving these effects.

In blocked stimulation designs, the picture is equally confusing. For example, Wastell & Kleinman conducted a pair of studies that highlight the effects of both paradigm and presentation rate on VEP adaptation (Wastell and Kleinman 1980; Wang, Iliescu et al. 2011). In varying the amount of time between stimulus presentations within a train of 10 trials, they showed significantly more adaptation (i.e. VEP attenuation) in “fast” conditions (500 & 1000ms ISIs) compared to “slow” conditions (2000 & 3000ms ISIs) (Wang, Iliescu et al. 2011). In the second of their studies, a paired-presentation design with monocular stimulation was employed and attenuation was observed in ipsilaterally and contralaterally elicited VEPs with an ISI of 1000ms (Wastell and Kleinman 1980). Still other studies failed to show any rapid adaptation effects in the visual domain in healthy controls or in patients with chronic schizophrenia when employing a paired-presentation paradigm (Adler 1985).

Clearly, much remains to be done to adequately characterize the adaptation properties of the human visual system. There is an added imperative to map visual adaptation properties as visual processing and sensory adaptation deficits may serve as strong candidate endophenotypes for various psychiatric disorders. In schizophrenia, for instance, the P1 component of the VEP is attenuated in first-episode drug naive patients, chronic patients, and their first degree unaffected relative (Foxe, Doniger et al. 2001; Yeap, Kelly et al. 2006; Yeap, Kelly et al. 2008). Furthermore, patients with schizophrenia consistently display altered auditory adaptation (Adler 1985; Potter, Summerfelt et al. 2006; Braff, Light et al. 2007; Patterson, Hetrick et al. 2008) but visual adaptation functions have yet to be closely interrogated in this population. Evidence is also emerging for visual-sensory processing abnormalities in individual with an autism spectrum disorder (Frey, Molholm et al. 2013). We believe that under adequately taxing conditions, a second-order measure of “dynamic”

early visual processing may offer a unique window into specific, observable short-term plasticity and sensory processing, with implications for characterizing psychiatric and neurodevelopmental disorders. However, before addressing deficits in a clinical population, the spatial and temporal profile of visual adaptation in the healthy visual system must be fully elucidated. Questions remain as to how quickly the VEP attenuates, which regions of the visual cortex show the greatest adaptation effects, when during the temporal evolution of the sensory processing period adaptation effects emerge, how different paradigms affect adaptation, how adaptation is affected by presentation rate, and how detectible all these changes are to non-invasive measuring techniques.

We examined these questions here in a pair of related experiments. Experiment 1 involved presenting pairs of stimuli with varying inter stimulus intervals (ISI) and comparing the amplitude of the VEP to the second stimulus to that of the first (paired-presentation) as a function of ISI. Experiment 2 involved presenting stimuli at a constant ISI in blocks of 100 stimuli, and then comparing the VEP amplitude across blocks for different ISIs (block-presentation). The major goals of this study were the following: 1) To assess whether visual adaptation can be assayed employing parameters similar to those used in somatosensory and auditory studies, as measured by the paired-presentation paradigm (Experiment 1); 2) Whether further taxation of the system in the block-presentation paradigm (Experiment 2) results in a differing adaption profile; 3) Whether studying second-order ‘dynamic’ characteristics of the brain, such as VEP adaptation changes elicited by different stimulus presentation rates and across various scalp sites would offer additional understanding of sensory processing in the visual system (Experiments 1 & 2); 4) Whether adaptation functions are robust enough to be statistically identified at the individual participant level; and 5) To employ inverse source-localization techniques to estimate the major cortical generators of adaptation effects.

METHODS

Participants

Eleven healthy adults (4 males, mean age=26, SD=3.6) completed Experiment 1. Fifteen healthy adults completed Experiment 2 (8 males, mean age=26, SD=4.4). Of the 15 participants in Experiment 2, three also completed Experiment 1. All had normal or corrected-to-normal vision. The experimental procedures were approved by the Institutional Review Board at Albert Einstein College of Medicine and conformed to the tenets of the Declaration of Helsinki. All participants provided written informed consent and received a modest fee.

Stimuli

Stimuli were 100% contrast black and white checkerboard annuli (6.5 cm diameter, 1cm width, $4^\circ \times 4^\circ$, white luminance of 120 cd/m², black luminance of 0.2 cd/m²) centered against a grey (luminance = 25 cd/m²) background. A fixation cross was always present on the screen, including during checkerboard presentation. The fixation cross changed color every 20–40s. Checkerboards were presented for 33ms and at different inter-stimulus-intervals (ISIs).

Procedure

Participants sat in a darkened sound-attenuated electrically shielded double-walled booth (Industrial Acoustics Company, Bronx, NY), 90 cm from a 34×55 cm LCD computer screen (ViewSonic VP2655wb, 60Hz refresh rate). They were instructed to minimize head movements and blinking while fixating on a red cross at the center of the screen. They performed a change detection task to ensure fixation in which they were asked to respond to fixation cross color changes (from red to green, lasting 40ms) with a mouse button press using the index finger of their dominant hand. The presentation of checkerboard stimuli was temporally unrelated to this central fixation task.

Paradigms

Experiment 1- Paired Presentation—Participants were presented with the checkerboard stimuli in pairs (first stimulus in pair = S1, second stimulus in pair = S2) with an ISI of either 200ms or 300ms. There was a 2500 ms interval between the paired presentations. A non-paired stimulus (i.e. a “catch” trial) was randomly presented one third of the time during a semi random time point (>2500ms) in the inter-pair interval. Subjects were exposed to approximately 300 presentations of each condition (pair with 200ms ISI, pair with 300ms ISI, and catch). Total run time for this experiment ranged from 45–60mins.

Experiment 2- Block Presentation—Checkerboards were presented in blocks of 100 stimuli. Within each block, the stimuli were centered at an ISI, around which the actual presentations were jittered by ± 50 ms. Five different ISIs were used: 200ms, 300ms, 550ms, 1050ms, and 2550ms. For example, the following sequence of ISIs might be typical of a segment of trials in the 300ms ISI condition: 272-267-304-320-336-300-288, etc. Between-block interval was self-paced, with participants allowed to move to the next block by pressing the spacebar on a keyboard 2500–5000ms after the last stimulus of the preceding block. Block presentation was pseudorandom. In total, participants experienced 4 blocks of each of the four shorter ISIs (200ms, 300ms, 550ms, 1050ms) and two blocks of the longest ISI (2550ms). Total run time for the experiment ranged from 35–45 minutes. For a schematic time course representation of Experiment 1 & Experiment 2, the reader is referred to Figure 1.

Data Acquisition

Continuous electroencephalographic (EEG) data were recorded in both experiments using a Biosemi ActiveTwo 168-channel electrode array, analog-to-digital converter, and fiber-optic pass-through to a dedicated data acquisition computer. The data were recorded at 512 Hz with a pass-band from DC to 150Hz. The continuous EEG was subsequently low-pass filtered at 45Hz (4th order-zero phase Butterworth filter, 27 dB/octave) and high-pass filtered at 1Hz (4th order-zero phase Butterworth filter, 24 dB/octave). Epochs of 600 ms with 100 ms prestimulus baseline were extracted from the continuous data. An automatic artifact rejection criterion of $\pm 75 \mu\text{V}$ was applied across all electrodes in the array. Trials with more than six artifact channels were rejected. In trials with less than six such channels, any remaining bad channels were interpolated using the nearest neighbor spline (Perrin,

Pernier et al. 1987; Gonzalez Andino, Grave de Peralta Menendez et al. 2001). The data were re-referenced to the average of all channels.

Pre-processing

Experiment 1: Catch-trial transformation—For the paired-presentation experiment (Experiment 1) waveforms for the S2 VEP were derived to isolate the responses to the S2 from the continued activity related to the S1, due to the short ISIs used. These waveforms were derived by subtracting the “catch” from the composite S1–S2 VEP and then shifting the isolated S2 response back in time by the appropriate delay. See Supplementary Figure 1 for an illustration of the catch-trial transformation. The subtraction allowed for the examination of the “pure” VEP response to the second stimulus in a pair without any interference from ongoing activity related to the first stimulus. There was an average acceptance rate of 74% of trials per condition for this experiment.

Experiment 2: Adjacent Response Algorithm (ADJAR)—As the timing between the stimuli of the shortest ISI was between 150 to 250ms, we implemented the Adjacent Response (ADJAR) algorithm on our subject-level data to model and remove any response overlap (Woldorff 1993; Grave de Peralta-Menendez and Gonzalez-Andino 1998). ADJAR correction was only applied to the 200ms ISI condition. See Supplementary Figure 2 for a depiction of data from the 200ms ISI condition before and after the ADJAR procedure. There was an average acceptance rate of 82% of trials per condition for this experiment.

Analysis Strategy

Identifying scalp-sites of interest and time windows for primary analysis—For each experiment, the data from all participants from each electrode were collapsed into a single averaged waveform. These group-averaged waveforms were visually inspected across all scalp sites, and the familiar components of the VEP were identified (Foxe and Simpson 2002). This allowed for definition of the precise timing of a given component and delineation of the scalp sites at which each component was of maximal amplitude. Evoked responses to these simple visual stimuli showed the typical sequence of VEP components (P1, N1, P2) over occipital sites. Following this procedure, three time-windows were identified for analysis corresponding to peak components over central-occipital (Oz), left occipital (PO7 & O1), and right occipital (O2 & PO8) sites: 90–110ms, 130–150ms, and 160–180ms.

Although the use of broadly defined component peaks is a good means of limiting the number of statistical tests that will be conducted, these components clearly represent the activity of many simultaneously active brain generators at any given moment (Foxe and Simpson 2002). In order to provide a more complete picture of the mechanisms underlying visual adaptation, we also present the scalp topographic maps for time period in which significant adaptation is observed and conduct a source modeling analysis (discussed below).

Primary Analysis—Statistical analyses were performed using custom MATLAB scripts (Mathworks), the Fieldtrip toolbox for EEG analysis (Oostenveld, Fries et al. 2011),

EEGLAB (Delorme and Makeig 2004), and the SPSS software package (SPSS). For the paired experiment (Experiment 1), a repeated-measures analysis of variance (ANOVA) with factors of stimulus order (S1, S2), ISI (200ms, 300ms) and scalp-site (PO7, O1, Oz, O2, PO8) was performed for each of the time periods of interest ($2 \times 2 \times 5$ ANOVA). For the block experiment (Experiment 2), a repeated-measures ANOVA with factors of ISI (200ms, 300ms, 550ms, 1050ms, 2550ms) and scalp-site (occipital/parieto-occipital sites: PO7, O1, Oz, O2, PO8) was performed for each of the time periods of interest (5×5 ANOVA). Significant effects were then examined using protected post-hoc contrasts. The Greenhouse-Geisser correction was used to adjust F values and probabilities when sphericity was violated; the original degrees of freedom are presented for each analysis.

Source Localization—In order to examine the brain generators for representative short and long ISI conditions, the data from experiment 2, which provided greater discrepancy between ISIs, was modeled using the **Local Auto Regressive Average** inverse solution (**LAURA**; (Gonzalez Andino, Grave de Peralta Menendez et al. 2001; Grave de Peralta Menendez, Gonzalez Andino et al. 2001) as implemented in the Cartool software by Denis Brunet (brainmapping.unige.ch/cartool). The linear distributed inverse solution is based on a realistic head model with 4024 solutions points equally distributed within the grey matter of the Montreal Neurological Institute's (MNI) average brain. The LAURA method deals with multiple simultaneously active sources of *a priori* unknown location, and makes no assumptions regarding the number or location of active sources. It selects the source configuration that best mimics the biophysical behavior of the electrical field and produces a unique estimation of the current source density inside the brain. That is, the estimated activity at one point depends on the activity at neighboring points as described by electromagnetic laws (Grave de Peralta-Menendez and Gonzalez-Andino 1998). Mean scalp topographies of the main periods of interest were down-sampled from the 168-channel montage to a 111-channel montage by means of a 3D-spline interpolation (Perrin, Pernier et al. 1987; Lopez, Mercier et al. 2011).

Source reconstruction was performed at two levels. First, we applied LAURA to VEP maps for the 300ms and 2550ms ISI conditions. Since there were minimal differences in the scalp topography for the 200, 300, 550ms ISIs (Figure 5), the 300ms ISIs served as a representative for the “shorter” ISIs. Additionally, the scalp topographies for the 1050 and 2550ms ISIs were also very similar, and so the 2550ms ISI served as a representative for the “longer” ISIs. With this, we were able to visualize the brain generators for the signals recorded under these two different presentation.

Second, we performed statistical analyses in the source space to test for regions sensitive to adaptation effects (i.e. regions distinguishing between “fast” and “slow” presentation rates). These theoretically play a role in modulating the differences observed in the VEPs across ISIs. To do so, we determined for each participant and each condition (300ms ISI and 2550ms ISI) at the three time periods of interest, the mean corresponding VEP map. The inverse solution was applied to each individual VEP map. The inverse solutions for the representative short and long ISIs were compared statistically (paired randomization tests), with subjects as a repeated measure. To correct for multiple comparisons we applied a

Bonferroni correction ($\alpha/\text{number of electrodes}$, $.05/160=.0003125$) which decreases the chances of Type I errors (Grave de Peralta Menendez, Gonzalez Andino et al. 2001).

Individual Participant Level Analysis—In experiment 2, in order to investigate the robustness of adaptation and the minimum number of sweeps required for statistical significance at the individual participant level we conducted a non-parametric randomization procedure (Maris and Oostenveld 2007). For each participant we compared the amplitude recorded under the 2500 ISI condition against each of the other ISI conditions (200, 300, 550, 1050ms) at the central occipital site for each of the time periods of interest (90–110, 130–150, 160–180ms). This scalp site was chosen for analysis as it demonstrated the largest activation and strongest modulation in the group-level statistics.

The observed difference between the 2550ms ISI and the test ISI was compared with a reference distribution of differences that was derived by iteratively randomizing between the two original data sets (i.e. individual-subject VEP amplitudes for the 2550ms and test ISI) 10,000 times. The number of epochs selected for the bootstrapping process was a subset of the total which increased in steps of 10 from 30 epochs until statistical significance or the maximum number of sweeps was reached (Nolan, Butler et al. 2012). A one-tailed threshold of $p < 0.05$ was used to define significance. The p value for a randomization test was calculated from the proportion of values in the reference difference distribution that exceeded the observed difference (Fiebelkorn, Foxe et al. 2011).

RESULTS

The checkerboard annulus evoked a VEP that exhibited a different morphology based on scalp site. Amplitudes were greatest over central occipital scalp. At the midline site (Oz) the first major VEP component had peak at ~110ms (negative going) and the next major component peaked at ~180ms (positive going). At the most proximal lateral sites (O1 & O2), the first major VEP component had a peak ~150ms (negative going) and the next major component peaked at around 250ms (positive going). At the more distal lateral sites (PO7 & PO8) the first major component had a peak at ~100ms (positive going) and the next major component peaked at ~160ms.

Experiment 1: Paired Presentation

Figure 2 shows the group averaged VEP waveforms for the 200ms (red) and 300ms (blue) ISIs, with the three time periods of interest highlighted by the opaque vertical grey boxes. These waveforms contain both the VEP elicited by the first stimulus in a pair (S1) as well as the VEP to the second stimulus (S2) in the pair. The figure also displays the VEP waveform elicited by the “catch” trials (black). This response should be entirely equivalent to the one evoked by the S1 stimulus. Also shown are the “derived” waveforms for the S2 VEP which isolate the responses to the S2 from the continued activity related to the S1. These waveforms were derived by subtracting the “catch” from the composite S1–S2 VEP and then shifting the isolated S2 response back in time by the appropriate delay (red-dashed for the 200ms and blue-dashed for the 300ms ISI). These waveforms are shown for the five scalp sites of interest (PO7, O1, Oz, O2, PO8) over occipital and parieto-occipital scalp regions. The reader is referred to Supplemental Fig 3A for an alternate depiction of these

tuning parameters. Contrary to what was expected, S2 response amplitudes appear greater than those to the S1, and this is most prominent over midline and right occipital scalp.

VEP Amplitudes—Results from the 3 main ANOVAs performed to examine the effect of ISI, stimulus order, scalp site, and any interactions at each of time periods of interest are presented in Table 1. In summary, the primary observation is a significant effect of order, with S2 VEP amplitudes larger than S1. This effect is primarily seen at lateral occipital sites for the two later time periods. This analysis captures the major negative going peak in the VEP at these sites, spanning from 130–180ms. At the midline site (Oz), this enhancement effect is seen during the first time window of analysis, which at this site captures the peak of the major negative going component (~100ms). The effect then reverses during the last time window of analysis, with S2 amplitudes attenuated compared to S1. Here the analysis captures the peak of a major positive going component in the VEP at 180ms.

Scalp Topographies—Scalp topographic maps representing interpolated potential distributions of the grand mean are shown for the Catch-trial, the 200ms ISI and the 300ms ISI conditions (columns) and the three periods of interest (rows) in Figure 3. The first row of topographical distributions for the 90–110ms period shows a strong central occipital distribution which is similar for both ISIs. The second row of topographical distributions for the 130–150ms period shows evidence for a somewhat more bilateral occipital distribution, with greater amplitude evident over right occipital scalp, and this activity shows clearly greater negativity for the S2 stimuli. The third row of topographical distributions for the 160–180ms time period of interest shows a positive central occipital distribution with an evident decrease in amplitude to the S2 stimuli. Further, these maps show indistinguishable topographic distributions for the S1 and catch trials, providing further evidence that they are a representation of the same process.

Experiment 2: Block Presentation

Figure 4A shows the group averaged VEP waveforms for the five ISIs at the five targeted scalp-sites over occipital and parieto-occipital areas with the three time periods of interest highlighted by the vertical grey boxes. Figure 5B is a more focused representation of the effects of ISI on VEP at each scalp site during the three time periods of interest. Together, these figures illustrate clear adaptation effects that vary as a function of ISI, scalp site, and time period of analysis. The most prominent effect is seen in the influence of ISI on the first major negative going response, with a more negative going response for longer ISI conditions. However, the midline occipital site also shows a second phase of adaptation, where a reversal of this effect is seen for the later major going positive component. The reader is referred to Supplemental Fig 3B for an alternate depiction of these tuning parameters, in which tuning functions are derived for each of the five scalp-sites using the group mean and standard error amplitude of the VEP for each ISI for the time periods of interest.

VEP Amplitudes—Results from the 3 main ANOVAs performed to examine the effect of ISI, scalp site, and any interactions at the three time periods of interest (90–110ms, 130–150ms and 160–180ms) are presented in Table 2. In summary, significant adaptation effects

are noted at all sites examined, with the major finding being that VEP amplitudes decrease with faster ISIs. This robust effect is noted during the later time windows, spanning 130–180ms, for the lateral occipital sites. At these sites (PO7, O1, PO8, O2) this time window captures the major negative going component of the VEP. For the midline site (Oz) the adaptation effect is also noted at the first negative going peak, which at this site occurs earlier and spans 110–140ms. The effect at Oz then reverses during the last time window of analysis, with VEP amplitudes increasing with faster ISIs. This time window captures the major positive-going component at this site, which peaks at ~180ms.

Scalp Topographies—Scalp topographic maps representing interpolated potential distributions are shown of the group mean for all ISI conditions (columns) during the three time periods of interest (rows) in Figure 5 *right*. The first row of topographical distributions for the 90–110ms time period shows a stronger focal midline occipital distribution which is similar for all ISIs in this time window. The second row of topographical distributions for the 130–150ms time period shows a progression of topographies with respect to the ISI, from a positive central occipital distribution for the shortest ISIs of 200ms to a negative bilateral occipital distribution for the longer ISIs of 1050 and 2550ms. The third row of topographical distributions for the 160–180ms time period of interest shows a progression of topographies from a positive central occipital distribution for the shortest ISI (200ms) to a negative bi-lateral occipital distribution for the longest ISI (2550ms).

Difference topographies were also computed by comparing the interpolated potential distributions for the 2550ms ISI condition against each of the other conditions (200ms, 300ms, 550ms, and 1050ms ISIs) for the later time periods which showed a significant effect of ISI on VEP amplitude (Figure 5 *left*). The difference scalp topographic maps for the 90–110ms timeframe (top row) show an emerging central negativity focus with the strongest difference signal seen when comparing the 2 most discrepant ISIs (2550 vs 200ms), as can be seen here though differences in this time window are weaker and also highly similar across ISIs. During the 130–150ms timeframe (second row), difference maps reveal a strong central-occipital negativity that is similar across the comparisons between the 2550ms ISI versus the 200ms, 300ms, and 550ms ISI, but weaker between the most similar ISIs (1050 vs 2550ms), confirming a similar activation profile for the 3 shorter ISIs, but a difference between short and long ISIs. The 160–180ms time frame (bottom row) revealed a similar strong central-occipital negativity for each comparison, which again was weakest for the 1050ms versus 2550ms subtraction. In summary, the three shorter ISIs exhibit a response pattern that is different from the two longest ISIs but relatively similar to each other. The 1050ms ISI response is unique as compared to the shorter ISIs and is most similar to the 2550ms condition, but still distinct. More modest differences in frontal activation are also noted in the topographic maps across time and ISI.

Source Localization—A source localization model was applied to better understand the generators of the adaptation effects seen in this experiment for the time period during which there was sufficient signal strength in the waveforms and difference topographies, depicted in Figure 6A. In the 90–110ms interval (top row) the main brain generators were localized bilaterally to regions in and surrounding the occipital pole, pointing to striate and extrastriate

generators in this timeframe for both the 300ms and 2550ms conditions. These sources encompassed parts of Brodmann area 17 (primary visual cortex), area 18 (parastriate visual association areas), and area 19 (extrastriate visual association areas). In the 130–150ms interval (middle row) brain activation extended into extrastriate areas (relative to the 90–110ms period) and included both dorsal and ventral visual regions (Brodmann 18 & 19). Additionally, the 2550ms ISI condition contained generators located more dorsal/superior in comparison to the 350ms ISI sources for this time period, but still including strong inferior occipital cortex activation. Additionally, there was minor activation of the middle temporal gyrus (including association areas in Brodmann 21 involved in object form and motion processing and temporal recognition) in the 2550ms condition in this time period.

In the 160–180ms time window (bottom row), the main generators for both conditions localized to more inferior occipital regions as compared with the previous time period. In the 300ms condition, sources were over Brodmann area 18 along with some activation over Brodmann area 7, which is part of the parietal cortex and involved in visuo-motor coordination. In the 2550ms condition there was inferior lateral activation involving the lingual gyrus and Brodmann area 19.

Randomization tests conducted to compare the signal sources identified above revealed significant differences between the two conditions for all three time periods, as can be seen in Figure 6B. In the 90–110ms time window, the differences were localized to the occipital lobule, superior parietal lobule, lingual gyrus, and medial frontal gyrus. Differences in the 130–150ms time window were most pronounced, spanning the middle temporal gyrus of the temporal lobe, the postcentral gyrus in the parietal lobe, and the superior frontal gyrus encompassing Brodmann area 8, which is involved in motor planning and encompasses the frontal eye fields. The 160–180ms time window revealed fewest significantly different sources across the two conditions. These were localized to frontal areas, including the middle frontal gyrus (Brodmann area 9) and the superior frontal gyrus.

Individual Participant Level Analyses—We sought to establish how robust these measures of adaptation were and to assess whether significant adaptation functions could be observed consistently at the individual participant level, since a major aim here is to develop this measure as a potential biomarker of disease. If it is to serve as such, it will be imperative that it is robust at the individual level. Individual participant randomization analysis was conducted comparing the longest ISI (2550ms) with each of the other ISIs (200ms, 300ms, 550ms, 1050ms) at the three time periods of interest at the central occipital electrode site (Oz) and two lateral sites (O1 & O2). Table 3 shows the number of participants exhibiting significant adaptation effects along with the average and standard deviation of the number of sweeps required for this effect, as a function of ISI. Overall, participants showed significant differences in amplitude between the most discrepant ISIs (i.e. 200, 300, and 550 vs 2550ms). For the middle time period of interest (130–150ms), all participants showed significant differences between the shortest (200ms ISI) and the longest (2550ms ISI) at the central occipital site. The 160–180ms time period contained the most stable effects across scalp sites and ISIs. During this period at least 14 of the 15 participants showed significant VEP amplitude differences for all of the ISI comparisons at Oz, all participants showed significant VEP differences for the two shorter ISIs (200 & 300ms) against the 2550ms ISI

at Oz & O2, and 13 out of 15 at O1. The individual participant analysis results are in line with the group statistics with the largest difference occurring at the later time periods.

Representative individual waveforms for three participants are depicted in Figure 7. VEPs to a 'fast' ISI condition (300ms) and 'slow' ISI condition (2550ms) are plotted for the central occipital site and the two lateral sites. Amplitude values along these waveforms were taken for each individual subject to conduct the analysis described above. Here it can be seen that even at the individual level modulations based on presentation rate are evident. The dashed line in this figure represents the difference in amplitude between these two conditions (fast vs. slow) and can be interpreted as an index of adaptation.

DISCUSSION

High-density VEPs were recorded in a pair of experiments to examine visual adaptation in healthy human adults as a function of presentation rate and of using a blocked versus a paired presentation approach. In Experiment 1, stimuli were presented in pairs with relatively fast ISIs of 200ms or 300ms. In Experiment 2, stimuli were presented in much longer blocks (100 stimuli/block) while ISI was parametrically manipulated across blocks (ISIs of 200ms, 300ms, 550ms, 1050ms, and 2550ms respectively). The data revealed clear evidence for adaptation during blocked presentations, with dramatic and consistent modulation of VEP amplitude as a function of presentation rate. In contrast, the paired stimulation approach resulted in more modest VEP amplitude changes and despite the fact that similarly fast ISIs were employed as in the blocked experiment there was no clear attenuation effect of the major VEP components across scalp sites. In fact, the effects reported for Experiment 1 were opposite to what are classically expected using paired-adaptation paradigms, where the typical finding is a decrease in amplitude of the evoked response to the repeated stimulus during the earliest phases of processing. A second major goal of the current study was to establish whether visual adaptation functions could be reliably observed at the individual participant level. This goal was realized, establishing a potentially powerful biomarker of visual sensory function for deployment in clinical populations. In what follows, we discuss the results of these experiments in further detail and their implications for future work.

Experiment 1- Paired-Presentation Paradigm

While on first consideration a lack of reduced VEP amplitude to the S2 might seem surprising, a close examination of the paired-presentation auditory adaptation literature reveals a more nuanced picture. At ISIs in the range of those used here, response enhancement rather than suppression has sometimes been observed (Budd and Michie 1994; Loveless, Levanen et al. 1996; Sable, Low et al. 2004; Wang, Mouraux et al. 2008). For instance, Loveless and colleagues demonstrated that the classic P50 attenuation effect seen in the AEP can be reversed if ISIs <400ms are employed (Loveless, Hari et al. 1989). This, however, is not always the case with both auditory and visual responses also showing attenuation to even shorter ISIs (<100ms) during both early and late stages of processing (Gawne, Osbourne et al. 2011). Alternatively, it is possible that certain short ISIs (40–90ms) fall within the refractory period of human visual neurons, with observed attenuation

occurring as a result of a decrease in the excitability of visual cortex and multiple stimuli being perceived as one (Musselwhite and Jeffreys 1983; Skrandies and Raile 1989; Coch, Skendzel et al. 2005).

Another variable that may contribute to apparently contradictory results for the short ISI across paradigms is whether random or blocked presentation of ISIs is employed. Here, the inter-pair interval randomly varied within the same block. Wang and colleagues have argued that S2 attenuation is seen only in blocks containing exclusively pairs of the same ISI (Wang, Mouraux et al. 2010). Their reasoning is that only when the timing of the second stimulus is constant is it “*nonnovel and highly predictable*”(p. 2119), thereby eliciting a reduced neural response. Thus if ISI for each pair is variable within a block, S2 suppression may not be seen since timing is somewhat more unpredictable. Such an explanation could account for the lack of attenuation seen in Experiment 1 during the early time windows of analysis. The later change from S2 enhancement to S2 attenuation as a result of processing stage reported here has also been previously observed in other sensory modalities (Wang, Mouraux et al. 2008). Wang and colleagues in a paired, random ISI design, report enhancement of the N1 wave and attenuation of the P2 wave for auditory and somatosensory stimuli when short ISIs were examined. Clearly, a greater range of ISIs and comparison of random versus blocked ISI rate will be necessary to fully characterize these functions in the visual system.

Experiment 2- Blocked-Presentation Paradigm

Comparable to what has been reported in the auditory and somatosensory literatures (Hamalainen, Kekoni et al. 1990; Pereira, Cardoso et al. 2014), ERP attenuation to repetitive stimulation, which was modulated by presentation rate was observed. In Exp 2 VEP attenuation was modulated by ISI, with faster presentation rates leading to smaller VEP amplitudes. Source analyses pointed to adaptation effects not only in early striate and extrastriate visual cortical areas, but also across a widespread network of higher order dorsal and ventral visual regions that extended into frontal cortex. Further, the most robust adaptation effects in the visual system occurred some 65 to 100 ms after initial response onset (Foxe and Simpson 2002), suggesting a more complex neurophysiological profile than previously assumed.

Whereas most ERP characterizations are conducted at the group level, a central aim of the current study was to quantify the individual subject reliability of these effects with the goal of developing a metric of visual processing that might prove useful as a biomarker. In the block-presentation paradigm (Experiment 2) the ISI-specific effects were measurable at both the group and individual level, most reliably seen starting at about 130ms (in 15 out of 15 participants), whereas for the paired-presentation paradigm (Experiment 1) only the group effects were significant.

Very few studies have comprehensively examined the effect of multiple ISIs (presentation rates) on sensory adaptation in the visual system. This is perhaps because the wide variety of presentation paradigms utilized in the study of adaptation has made it difficult to elucidate a clear effect of stimulus repetition on the VEP amplitude. Here we find that a block-paradigm such as used in Experiment 2 is well-suited for investigations of short-term visual

adaptation. Our data establish that adaptive filtering of repetitive visual stimulation is reliably characterized by 1) Challenging the visual system with increased repetition and, 2) Thoroughly probing across stages of visual processing and scalp sites. In contrast, the short-term plasticity mechanisms assayed in Experiment 2 are not adequately engaged in the paired-paradigm (Experiment 1).

The analysis approach presented in this paper provides a composite measure of overall adaptation across an entire block (i.e. a period of 100 stimuli) and compares this adaptation *between* the various ISIs. However, the question as to when during the 100 stimuli in a given block the adaptation function stabilizes is one that our study was not designed to address (i.e. *within* block adaptation). Taken together, the results from Experiment 1 and Experiment 2, suggest that certainly more than two trials are needed for adaptation to equilibrate. Post-hoc analysis of the data from Experiment 2 indicate that it might be possible to adequately represent adaptation with sequences much shorter than 100 stimuli – likely in the range of 10 stimuli per train (see Supplementary Figure 4). Thus, a shorter version of the experiment run on considerably greater numbers of individuals would allow for a much finer titration of the temporal course of adaptation in trains of stimuli, while contributing to “normative data” against which clinical populations may be assessed, a matter for future work.

Lastly, source localizations of the effects uncovered during the block experiment provide clues as to the potential mechanisms involved in this form of short-term sensory plasticity. It is noteworthy for instance that the adaptation effects uncovered here were not restricted to early striate and extrastriate regions, as one might initially expect with such a basic sensory assay. Rather, sources well beyond V1/V2 were differentially impacted by the varying presentation rates, including regions in both the dorsal and ventral streams, suggesting that adaptation impacts processing in regions within both superior parietal cortex and the lateral occipital complex. It is perhaps surprising that adaptation should be seen in these higher-order regions for the simple stimuli used, especially since the stimuli were not task-relevant and were essentially ignored by the participants. Studies employing task-relevant stimuli, examining orientation adaptation, have also found response modulation in areas beyond V1 in both human (Fang, Murray et al. 2005; Brunet, Bosman et al. 2014) and non-human participants (Hudson, Schiff et al. 2009; Wang, Iliescu et al. 2011). In these, changes in neuronal synchronization, both local and between regions, have been implicated in the main findings. Understanding the role and mechanisms underlying the involvement of higher-order regions in the current adaptation paradigm is an important matter for future work.

Future Directions

It is clear that the mechanistic and molecular underpinnings of basic adaptation are not yet fully understood. These mechanisms might differ between sensory modalities taking into account inherent differences in disparate neuronal populations such as response, recovery, and sampling rates. Studies employing pharmacologic manipulations and measuring changes under both the paired-presentation and the block-presentation paradigms along with studies using the same paradigms across different sensory modalities may reveal whether the adaptation profile is consistent across paradigms and whether sensory adaptation dynamics are modality-specific.

A more complete understanding of sensory adaptation may follow from pharmacological studies targeting neurotransmitter systems implicated in adaptation. Studies assessing molecular mechanisms of adaptation in the auditory system are sparse and provide varying findings. There are reports of serotonergic (Oranje, Wienberg et al. 2011), dopaminergic (Light, Malaspina et al. 1999), and nicotinic effects (Knott, Fisher et al. 2010) on auditory adaptation. In the visual system, one group conducted an experiment in which light deprivation, which according to the authors down-regulates the gabaergic system, lead to adaptation impairments (Palermo, Giglia et al. 2011). These impairments were reversed with exposure to high frequency repeated transcranial magnetic stimulation (rTMS), which had previously been shown to reverse light deprivation inhibitory effects.

An additional research question concerns the effects of attention on sensory adaptation. Recent studies have attempted to examine this interaction, and although the findings are still equivocal, there is some evidence for attention-modulated auditory adaptation (Rosburg, Trautner et al. 2009; Gjini, Burroughs et al. 2011). This is of particular interest for both the characterization of adaptation in the general population, and in clinical groups, particularly those with documented attention deficits (i.e. schizophrenia, autism, etc).

A primary motivation for the current study was to examine whether visual adaptation to varying presentation rates would be used to elicit a robust metric of short-term visual plasticity, one that could ultimately be deployed as a sensitive assay of visual function in clinical populations. Our interest was specifically whetted by the fact that abnormal sensory adaptation functions have been repeatedly demonstrated in patients with schizophrenia, but these have been assayed almost exclusively using auditory stimulation (Patterson, Hetrick et al. 2008; Olincy, Braff et al. 2010), although there is emerging evidence for related deficits in the somatosensory system (Thoma, Hanlon et al. 2007). Auditory adaptation deficits represent potentially powerful biomarkers of schizophrenia since they are also seen in a significant proportion of unaffected first-degree biological relatives of patients (Olincy, Braff et al. 2010). In a series of experiments, we have shown that visual sensory processing deficits are particularly robust in patients with schizophrenia (Foxy, Doniger et al. 2001; Doniger, Foxy et al. 2002; Foxy, Murray et al. 2005; Lalor, Yeap et al. 2008; Yeap, Kelly et al. 2008; Lalor, De Sanctis et al. 2012), a finding that has been observed across multiple labs (Mukundan 1986; Spencer, Nestor et al. 2004; Haenschel, Bittner et al. 2007). Crucially, these deficits are also seen in first-degree relatives (Yeap, Kelly et al. 2006), first-episode drug naïve patients (Yeap, Kelly et al. 2008) and in young adults with high schizotypy (Koychev, El-Deredy et al. 2010; Bedwell, Chan et al. 2013), pointing to their potential utility as risk endophenotypes (Gottesman and Gould 2003; Magno, Yeap et al. 2008; Foxy, Yeap et al. 2011).

A drawback of many of these studies, however, is that despite between-group effect sizes that are typically large, intrinsic inter-individual variability in the amplitude and morphology of the VEP response reduces their effectiveness as potential classifiers. We have made the argument that one way to surmount this issue of inter-individual variance is to assay second-order dynamic effects of sensory systems such as short-term plasticity, as with the visual adaptation paradigm at hand. It is of note that dysfunctional sensory plasticity has recently been shown in patients with schizophrenia (Cavus, Reinhart et al. 2012; Foxy, Yeap et al.

2013). Of course, if any given metric of sensory processing is ultimately to serve as a diagnostically meaningful biomarker, it must be possible to assay it robustly at the individual patient level, and it is very encouraging that this is precisely what was found here for block-presentation paradigm. Thus, if short-term sensory plasticity is impaired in patients with schizophrenia, mapping visual adaptation functions such as those detailed here may yet prove a very powerful method of assaying said dysfunction.

CONCLUSIONS

Adaptation of brain responses to repetitive stimulation is considered a fundamental property of sensory processing. Here we employed high-density EEG in two variants of an adaptation design, examining the effect of presentation rate on VEP attenuation in a paired-paradigm and a block-paradigm. Robust VEP modulations were evident as a function of presentation rate in the block-paradigm, with strongest modulations seen in the 130–150ms and 160–180ms phases of visual processing. In the paired design, we observed a more modest enhancement effect, with VEP amplitudes increasing when comparing S2 to S1. In order to better characterize the spatial and temporal properties of visual adaptation we used the full set of information collected from our high-density array to create scalp topographic maps and model the neural generators of adaptation across time. These analyses revealed sources in striate, extrastriate, and higher-order (e.g. superior temporal and lateral occipital) cortex. Importantly, in the block paradigm, adaptation effects were statistically robust at the individual participant level. These results suggest that a taxing paradigm, such as the current block-paradigm, is better suited to engage adaptation mechanisms in the visual system compared to a paired design. The increased sensitivity of the visual processing metric obtained in the block-paradigm has implications for the examination of visual processing deficits in clinical populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by a grant from the U.S. National Institute of Mental Health (NIMH) to JJF and SM (RO1 - MH085322). The authors would like to express their gratitude to Ms. Sarah Ruberman and Mr. Frantzy Acluche for their many hours of work in support of this study. The Human Clinical Phenotyping Core, where the participants enrolled in this study were recruited and evaluated, is a facility of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (RFK-IDDRC) which is funded by a center grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD P30 HD071593). Ongoing support of The Cognitive Neurophysiology Laboratory is provided through a grant from the Sheryl and Daniel R. Tishman Charitable Foundation.

References

- Adler LEW, MC, Freedman R. Neurophysiologic Studies of Sensory Gating in Schizophrenia: Comparison of Auditory and Visual Responses. *Biol Psychiatry*. 1985; 20:1284–1296. [PubMed: 4063418]
- Arnfred SM, Eder DN, et al. Gating of the vertex somatosensory and auditory evoked potential P50 and the correlation to skin conductance orienting response in healthy men. *Psychiatry Res*. 2001; 101(3):221–235. [PubMed: 11311925]

- Bedwell JS, Chan CC, et al. Changes in the visual-evoked P1 potential as a function of schizotypy and background color in healthy young adults. *J Psychiatr Res.* 2013; 47(4):542–547. [PubMed: 23369336]
- Braff DL, Light GA, et al. Prepulse inhibition and P50 suppression are both deficient but not correlated in schizophrenia patients. *Biol Psychiatry.* 2007; 61(10):1204–1207. [PubMed: 17161386]
- Brockhaus-Dumke A, Mueller R, et al. Sensory gating revisited: Relation between brain oscillations and auditory evoked potentials in schizophrenia. *Schizophrenia Research.* 2008; 99(1–3):238–249. [PubMed: 18160261]
- Brunet NM, Bosman CA, et al. Stimulus repetition modulates gamma-band synchronization in primate visual cortex. *Proc Natl Acad Sci U S A.* 2014; 111(9):3626–3631. [PubMed: 24554080]
- Budd TW, Barry RJ, et al. Decrement of the N1 auditory event-related potential with stimulus repetition: habituation vs. refractoriness. *Int J Psychophysiol.* 1998; 31(1):51–68. [PubMed: 9934621]
- Budd TW, Michie PT. Facilitation of the N1 Peak of the Auditory Erp at Short Stimulus Intervals. *Neuroreport.* 1994; 5(18):2513–2516. [PubMed: 7696592]
- Carlen M, Meletis K, et al. A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Molecular Psychiatry.* 2012; 17(5):537–548. [PubMed: 21468034]
- Cattan S, Bachatene L, et al. Comparative analysis of orientation maps in areas 17 and 18 of the cat primary visual cortex following adaptation. *Eur J Neurosci.* 2014; 40(3):2554–2563. [PubMed: 24827700]
- Cavus I, Reinhart RM, et al. Impaired visual cortical plasticity in schizophrenia. *Biol Psychiatry.* 2012; 71(6):512–520. [PubMed: 22364738]
- Chang WP, Arfken CL, et al. Probing the relative contribution of the first and second responses to sensory gating indices: a meta-analysis. *Psychophysiology.* 2011; 48(7):980–992. [PubMed: 21214588]
- Chung S, Li X, et al. Short-term depression at thalamocortical synapses contributes to rapid adaptation of cortical sensory responses in vivo. *Neuron.* 2002; 34(3):437–446. [PubMed: 11988174]
- Coch D, Skendzel W, et al. Auditory and visual refractory period effects in children and adults: an ERP study. *Clin Neurophysiol.* 2005; 116(9):2184–2203. [PubMed: 16043399]
- Davis H, Osterhammel PA, et al. Slow vertex potentials: interactions among auditory, tactile, electric and visual stimuli. *Electroencephalogr Clin Neurophysiol.* 1972; 33(6):537–545. [PubMed: 4117331]
- Delorme A, Makeig S. EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J Neurosci Methods.* 2004; 134(1):9–21. [PubMed: 15102499]
- Doniger GM, Foxe JJ, et al. Impaired visual object recognition and dorsal/ventral stream interaction in schizophrenia. *Arch Gen Psychiatry.* 2002; 59(11):1011–1020. [PubMed: 12418934]
- Fang F, Murray SO, et al. Orientation-tuned fMRI adaptation in human visual cortex. *J Neurophysiol.* 2005; 94(6):4188–4195. [PubMed: 16120668]
- Fiebelkorn IC, Foxe JJ, et al. Ready, set, reset: stimulus-locked periodicity in behavioral performance demonstrates the consequences of cross-sensory phase reset. *J Neurosci.* 2011; 31(27):9971–9981. [PubMed: 21734288]
- Foxe JJ, Doniger GM, et al. Early visual processing deficits in schizophrenia: impaired P1 generation revealed by high-density electrical mapping. *Neuroreport.* 2001; 12(17):3815–3820. [PubMed: 11726801]
- Foxe JJ, Murray MM, et al. Filling-in in schizophrenia: a high-density electrical mapping and source-analysis investigation of illusory contour processing. *Cereb Cortex.* 2005; 15(12):1914–1927. [PubMed: 15772373]
- Foxe JJ, Simpson GV. Flow of activation from V1 to frontal cortex in humans. A framework for defining “early” visual processing. *Exp Brain Res.* 2002; 142(1):139–150. [PubMed: 11797091]
- Foxe JJ, Yeap S, et al. Brief monocular deprivation as an assay of short-term visual sensory plasticity in schizophrenia -- “the binocular effect”. *Frontiers in Psychiatry.* 2013; 4

- Foxe JJ, Yeap S, et al. The N1 auditory evoked potential component as an endophenotype for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives, first-episode, and chronic schizophrenia patients. *Eur Arch Psychiatry Clin Neurosci*. 2011; 261(5): 331–339. [PubMed: 21153832]
- Frey HP, Molholm S, et al. Atypical cortical representation of peripheral visual space in children with an autism spectrum disorder. *Eur J Neurosci*. 2013; 38(1):2125–2138. [PubMed: 23692590]
- Friston K. A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci*. 2005; 360(1456):815–836. [PubMed: 15937014]
- Fruhstorfer H, Soveri P, et al. Short-term habituation of the auditory evoked response in man. *Electroencephalogr Clin Neurophysiol*. 1970; 28(2):153–161. [PubMed: 4189933]
- Gawne TJ, Osbourne TS, et al. Robust sensory gating in the cortical visual evoked potential using two spatially separated stimuli. *Clin Neurophysiol*. 2011; 122(3):588–593. [PubMed: 20709595]
- Gjini K, Burroughs S, et al. Relevance of attention in auditory sensory gating paradigms in schizophrenia A pilot study. *J Psychophysiol*. 2011; 25(2):60–66. [PubMed: 22140292]
- Gjini K, Sundaresan K, et al. Electroencephalographic evidence of sensory gating in the occipital visual cortex. *Neuroreport*. 2008; 19(15):1519–1522. [PubMed: 18797309]
- Gonzalez Andino SL, Grave de Peralta Menendez R, et al. Non-stationary distributed source approximation: an alternative to improve localization procedures. *Hum Brain Mapp*. 2001; 14(2): 81–95. [PubMed: 11500992]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160(4):636–645. [PubMed: 12668349]
- Grave de Peralta-Menendez R, Gonzalez-Andino SL. A critical analysis of linear inverse solutions to the neuroelectromagnetic inverse problem. *IEEE Trans Biomed Eng*. 1998; 45(4):440–448. [PubMed: 9556961]
- Grave de Peralta Menendez R, Gonzalez Andino S, et al. Noninvasive localization of electromagnetic epileptic activity. I. Method descriptions and simulations. *Brain Topogr*. 2001; 14(2):131–137. [PubMed: 11797811]
- Grill-Spector K, Henson R, et al. Repetition and the brain: neural models of stimulus-specific effects. *Trends Cogn Sci*. 2006; 10(1):14–23. [PubMed: 16321563]
- Grzeschik R, Bockmann-Barthel M, et al. Direction-specific adaptation of motion-onset auditory evoked potentials. *Eur J Neurosci*. 2013; 38(4):2557–2565. [PubMed: 23725339]
- Haenschel C, Bittner RA, et al. Contribution of impaired early-stage visual processing to working memory dysfunction in adolescents with schizophrenia: a study with event-related potentials and functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2007; 64(11):1229–1240. [PubMed: 17984392]
- Hamalainen H, Kekoni J, et al. Human somatosensory evoked potentials to mechanical pulses and vibration: contributions of SI and SII somatosensory cortices to P50 and P100 components. *Electroencephalogr Clin Neurophysiol*. 1990; 75(2):13–21. [PubMed: 1688769]
- Hetrick WP, Sandman CA, et al. Gender differences in gating of the auditory evoked potential in normal subjects. *Biol Psychiatry*. 1996; 39(1):51–58. [PubMed: 8719126]
- Hudson AE, Schiff ND, et al. Attentional modulation of adaptation in V4. *Eur J Neurosci*. 2009; 30(1): 151–171. [PubMed: 19558603]
- Knott VJ, Fisher DJ, et al. Differential effects of nicotine on P50 amplitude, its gating, and their neural sources in low and high suppressors. *Neuroscience*. 2010; 170(3):816–826. [PubMed: 20643194]
- Koychev I, El-Deredy W, et al. Visual information processing deficits as biomarkers of vulnerability to schizophrenia: an event-related potential study in schizotypy. *Neuropsychologia*. 2010; 48(7): 2205–2214. [PubMed: 20412812]
- Lalor EC, De Sanctis P, et al. Visual sensory processing deficits in schizophrenia: is there anything to the magnocellular account? *Schizophr Res*. 2012; 139(1–3):246–252. [PubMed: 22704644]
- Lalor EC, Yeap S, et al. Dissecting the cellular contributions to early visual sensory processing deficits in schizophrenia using the VESPA evoked response. *Schizophr Res*. 2008; 98(1–3):256–264. [PubMed: 17996424]
- Lanting CP, Briley PM, et al. Mechanisms of adaptation in human auditory cortex. *J Neurophysiol*. 2013; 110(4):973–983. [PubMed: 23719212]

- Light GA, Malaspina D, et al. Amphetamine disrupts P50 suppression in normal subjects. *Biol Psychiatry*. 1999; 46(7):990–996. [PubMed: 10509182]
- Lopez C, Mercier MR, et al. Spatiotemporal dynamics of visual vertical judgments: early and late brain mechanisms as revealed by high-density electrical neuroimaging. *Neuroscience*. 2011; 181:134–149. [PubMed: 21315805]
- Loveless N, Hari R, et al. Evoked-Responses of Human Auditory-Cortex May Be Enhanced by Preceding Stimuli. *Electroencephalogr Clin Neurophysiol*. 1989; 74(3):217–227. [PubMed: 2470578]
- Loveless N, Levanen S, et al. Temporal integration in auditory sensory memory: neuromagnetic evidence. *Electroencephalogr Clin Neurophysiol*. 1996; 100(3):220–228. [PubMed: 8681863]
- Magno E, Yeap S, et al. Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia. *Biol Psychiatry*. 2008; 64(5):385–391. [PubMed: 18472090]
- Maris E, Oostenveld R. Nonparametric statistical testing of EEG- and MEG-data. *J Neurosci Methods*. 2007; 164(1):177–190. [PubMed: 17517438]
- McLaughlin DF, Kelly EF. Evoked-Potentials as Indexes of Adaptation in the Somatosensory System in Humans - a Review and Prospectus. *Brain Research Reviews*. 1993; 18(2):151–206. [PubMed: 8339106]
- Megela AL, Teyler TJ. Habituation and the human evoked potential. *J Comp Physiol Psychol*. 1979; 93(6):1154–1170. [PubMed: 521525]
- Mukundan CR. Middle latency components of evoked potential responses in schizophrenics. *Biol Psychiatry*. 1986; 21(11):1097–1100. [PubMed: 3741925]
- Muller-Gass A, Marcoux A, et al. The effects of very slow rates of stimulus presentation on event-related potential estimates of hearing threshold. *International Journal of Audiology*. 2008; 47(1):34–43. [PubMed: 18196485]
- Musselwhite MJ, Jeffreys DA. Visual evoked potentials to double-pulse pattern presentation. *Vision Res*. 1983; 23(2):135–143. [PubMed: 6868388]
- Nolan H, Butler JS, et al. "Neural correlates of oddball detection in self-motion heading: a high-density event-related potential study of vestibular integration. *Experimental Brain Research*. 2012; 219(1):1–11. [PubMed: 22434342]
- Olincy A, Braff DL, et al. Inhibition of the P50 cerebral evoked response to repeated auditory stimuli: results from the Consortium on Genetics of Schizophrenia. *Schizophr Res*. 2010; 119(1–3):175–182. [PubMed: 20382002]
- Oostenveld R, Fries P, et al. FieldTrip: Open source software for advanced analysis of MEG, EEG, and invasive electrophysiological data. *Comput Intell Neurosci*. 2011; 2011:156869. [PubMed: 21253357]
- Oranje B, Wienberg M, et al. A single high dose of escitalopram disrupts sensory gating and habituation, but not sensorimotor gating in healthy volunteers. *Psychiatry Res*. 2011; 186(2–3):431–436. [PubMed: 20971512]
- Orekhova EV, Stroganova TA, et al. Sensory gating in young children with autism: relation to age, IQ, and EEG gamma oscillations. *Neurosci Lett*. 2008; 434(2):218–223. [PubMed: 18313850]
- Palermo A, Giglia G, et al. Does habituation depend on cortical inhibition? Results of a rTMS study in healthy subjects. *Exp Brain Res*. 2011; 212(1):101–107. [PubMed: 21537965]
- Patterson JV, Hetrick WP, et al. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Res*. 2008; 158(2):226–247. [PubMed: 18187207]
- Pereira DR, Cardoso S, et al. Effects of inter-stimulus interval (ISI) duration on the N1 and P2 components of the auditory event-related potential. *Int J Psychophysiol*. 2014
- Perrin F, Pernier J, et al. Mapping of scalp potentials by surface spline interpolation. *Electroencephalogr Clin Neurophysiol*. 1987; 66(1):75–81. [PubMed: 2431869]
- Potter D, Summerfelt A, et al. Review of clinical correlates of P50 sensory gating abnormalities in patients with schizophrenia. *Schizophr Bull*. 2006; 32(4):692–700. [PubMed: 16469942]
- Rosburg T, Trautner P, et al. Attention effects on sensory gating--intracranial and scalp recordings. *Neuroimage*. 2009; 48(3):554–563. [PubMed: 19576991]

- Rosburg T, Zimmerer K, et al. Short-term habituation of auditory evoked potential and neuromagnetic field components in dependence of the interstimulus interval. *Experimental Brain Research*. 2010; 205(4):559–570. [PubMed: 20711562]
- Roth WT, Krainz PL, et al. Parameters of temporal recovery of the human auditory evoked potential. *Electroencephalogr Clin Neurophysiol*. 1976; 40(6):623–632. [PubMed: 57048]
- Sable JJ, Low KA, et al. Latent inhibition mediates N1 attenuation to repeating sounds. *Psychophysiology*. 2004; 41(4):636–642. [PubMed: 15189486]
- Skrandies W, Raile A. Cortical and retinal refractory periods in the human visual system. *Int J Neurosci*. 1989; 44(1–2):185–195. [PubMed: 2562053]
- Spencer KM, Nestor PG, et al. Neural synchrony indexes disordered perception and cognition in schizophrenia. *Proc Natl Acad Sci U S A*. 2004; 101(49):17288–17293. [PubMed: 15546988]
- Thoma RJ, Hanlon FM, et al. Impaired secondary somatosensory gating in patients with schizophrenia. *Psychiatry Res*. 2007; 151(3):189–199. [PubMed: 17412427]
- Wang AL, Mouraux A, et al. The Enhancement of the N1 Wave Elicited by Sensory Stimuli Presented at Very Short Inter-Stimulus Intervals Is a General Feature across Sensory Systems. *PLoS ONE*. 2008; 3(12):e3929. [PubMed: 19081790]
- Wang AL, Mouraux A, et al. Stimulus novelty, and not neural refractoriness, explains the repetition suppression of laser-evoked potentials. *J Neurophysiol*. 2010; 104(4):2116–2124. [PubMed: 20592123]
- Wang Y, Iliescu BF, et al. Adaptive changes in neuronal synchronization in macaque V4. *J Neurosci*. 2011; 31(37):13204–13213. [PubMed: 21917803]
- Wastell DG, Kleinman D. A psychoanatomical investigation of the locus of the mechanism responsible for the refractoriness of the visual vertex potential. *Perception & Psychophysics*. 1980; 27(2):149–152.
- Woldorff MG. Distortion of Erp Averages Due to Overlap from Temporally Adjacent Erps - Analysis and Correction. *Psychophysiology*. 1993; 30(1):98–119. [PubMed: 8416067]
- Yeap S, Kelly SP, et al. Visual sensory processing deficits in Schizophrenia and their relationship to disease state. *Eur Arch Psychiatry Clin Neurosci*. 2008; 258(5):305–316. [PubMed: 18504634]
- Yeap S, Kelly SP, et al. Early visual sensory deficits as endophenotypes for schizophrenia: high-density electrical mapping in clinically unaffected first-degree relatives. *Arch Gen Psychiatry*. 2006; 63(11):1180–1188. [PubMed: 17088498]
- Yeap S, Kelly SP, et al. Visual sensory processing deficits in first-episode patients with Schizophrenia. *Schizophr Res*. 2008; 102(1–3):340–343. [PubMed: 18485671]
- Zucker RS. Short-term synaptic plasticity. *Annu Rev Neurosci*. 1989; 12:13–31. [PubMed: 2648947]

Figure 1.

Schematic diagram illustrating the two paradigms. **A.** Depiction of the paired-presentation paradigm used in Experiment 1. Stimuli were presented in pairs with an inter-stimulus interval of either 200 or 300ms and a long inter-pair interval of 2500ms. Catch trials, consisting of unpaired checkerboards, were presented one third of the time and were used to extract the isolated response to the second stimulus in a pair. **B.** Depiction of the block-presentation paradigm used in Experiment 2. Stimuli were presented in blocks of 100 trials, at an inter-stimulus interval centered around ISIs of 200, 300, 550, 1050, or 2550ms. The stimulus presentation was jittered by +/-50ms to allow for the implementation of an ADJAR procedure which models and removes response overlap (used in the 200ms condition).

Figure 2.

Waveforms obtained from subtracting the catch trials from the 200 and 300ms trials. The catch serves as the pure response to a single stimulus presentation (S1) and the trial waveform minus the catch represents the 'isolated' response to the second stimulus (S2). At 140ms there is an effect of order, with VEPs to the S2 being greater than to the S1. At 170ms, the effect reverses, with VEPs to the S2 being smaller (less positive) than to the S1. However, neither of these effects depends on ISI.

Figure 3.

Scalp topographic maps for the paired-paradigm reveal a difference between the first and second stimulus presentations and between the second and the catch for both ISIs. Additionally there is a clear difference in topography when comparing the response at 100 and 140ms (strong negativity) with the response at 170ms (strong positivity).

Figure 4.

A. Average waveforms for each of the five ISI conditions (Experiment 2) are displayed for the five occipital and occipito-parietal scalp sites of interest. A clear effect of ISI on VEP amplitude can be seen between 100–200ms, with slower stimulus presentation rates leading to greater absolute VEP amplitude. **B.** Amplitude by ISI plots. The effect of ISI on VEP amplitude at each scalp site for the three time periods of interest. The greatest adaptation based on ISI is seen in the later timewindows (130–150ms & 160–180ms) and is most robust at the central occipital site. Additionally, the directionality of adaptation by ISI at the central site (Oz) is exclusively reversed in the last time period of interest, with the slowest ISI here eliciting the smallest VEP amplitudes.

Figure 5.

Left - Scalp topographic maps reveal similar central-occipital negativity for the early time period across ISIs in the block-presentation. At the later time points the voltage distribution diverges, with the shorter ISIs showing central-occipital positivity and the longer ISIs a bilateral negativity. *Right*- Scalp topographic maps depicting the difference in electrical activation when comparing the 2550ms condition to each of the other ISIs. The difference topography is most unique when comparing electrical activation across the scalp when comparing the 1050ms ISI to the 2050ms ISI at 140 & 180ms post stimulus presentation.

Figure 6.

A. Brain generators estimated using a distributed linear inverse solution on the local autoregressive average for block-design. Early sources are mainly over occipital cortex, with later sources extending over parietal and temporal cortex. **B.** Randomization tests reveal significant differences in brain generators between the 300ms and 2550ms conditions. At 90–110ms these differences are mostly occipital. At 130–150ms the differences are most pronounced and expand over occipital, parietal, temporal and frontal areas, including superior parietal cortex and lateral occipital cortex. At 160–180ms, the only significantly different sources are frontal.

Figure 7.

Representative individual participant visual evoked potential waveforms. VEP to a 'fast' ISI condition (300ms) and 'slow' ISI condition (2550ms) is plotted for the central occipital site. The dashed line represents the difference in amplitude between these two conditions and can be interpreted as an index of adaptation.

Table 1

Experiment 1

A. Main ANOVA results summary for Experiment 1 (paired presentation).				
Experiment 1 - Paired Presentation				
	90–110ms	130–150ms	160–180ms	
ISI	n.s.	n.s.	n.s.	
Order	$F(1, 10)=17.725, p=0.002$ S2 amplitude>S1 amplitude	$F(1, 10)=19.859, p=0.001$	$F(1, 10)=13.609, p=0.004^{\dagger}$	
Scalp site	$F(4, 40)=7.997, p<0.004^{\dagger}$ Midline amplitudes > lateral sites	$F(4, 40)=2.692, p=0.045$	$F(4, 40)=4.554, p=0.015^{\dagger}$	
ISI x Order	n.s.	n.s.	n.s.	
ISI x Scalp site	n.s.	n.s.	n.s.	
Order x Scalp site	n.s.	$F(4, 40)=4.071, p=0.007$ S2 amplitude > S1 amplitude, greatest differences at midline, lessens more laterally	$F(4, 40)=5.038, p=0.002$ S1 amplitude > S2 amplitude but only at midline, all other lateral sites S2 > S1	
ISI x Order x Scalp site	n.s.	n.s.	n.s.	

B. Post-hoc comparisons for Experiment 1 (paired paradigm). Italics indicate a significant effect of ISI at that scalp site. Refer to Table 1A for interpreting the directionality of these effects.

Post-hoc t-tests					
Time	Scalp Site	PO7	O1	Oz	O2
90–110ms		n.s.	$t(21)=3.755, p=.001$	$t(21)=4.665, p<.001$	n.s.
130–150ms		n.s.	$t(21)=2.957, p=.008$	$t(21)=8.525, p<.001$	$t(21)=4.479, p<.001$
160–180ms		n.s.	$t(21)=3.828, p=.001$	$t(21)=7.294, p<.001$	$t(21)=3.862, p=.001$

Table 2

Experiment 2

A. Main ANOVA results summary for Experiment 2 (block-presentation).						
Experiment 2 - Block Presentation						
	90–110ms	130–150ms	160–180ms			
ISI	n.s.	$F(4, 56)=15.561, p<0.001^\dagger$	$F(4, 56)=24.573,$			
Scalp site	$F(4, 56)=15.956, p<0.001^\dagger$	$F(4, 56)=6.335, p=0.003^\ddagger$	$F(4, 56)=12.114, p<0.0001^\dagger$			
ISI x Scalp site	$F(16, 224)= 3.400, p=0.005^\ddagger$ Adaptation at midline & O1: Shorter ISIs = smaller VEPs	$F(16, 224)=7.175, p<0.001^\dagger$ Adaptation strongest at midline, but seen everywhere: shorter ISIs = smaller VEPs	$F(16, 224)=6.817, p<0.0001^\dagger$ Midline: longer ISIs = smaller VEPs All other lateral sites, shorter ISIs = smaller VEPs			
B. Post-hoc comparisons for Experiment 2 (block paradigm). Italics indicate a significant effect of ISI at that scalp site. Refer to Table 2A for interpreting the directionality of these effects.						
Repeated Measures Post-hoc ANOVA						
Time	Scalp Site	PO7	O1	Oz	O2	PO8
90–110ms		n.s.	$F(4,56)= 4.209, p=.024^\dagger$	$F(4,56)= 4.957, p=.014^\dagger$	n.s.	n.s.
130–150ms		$F(4,56)= 6.083, p=.007^\ddagger$	$F(4,56)= 15.447, p<.001^\dagger$	$F(4,56)= 20.017, p<.001^\dagger$	$F(4,56)= 14.095, p<.001^\dagger$	$F(4,56)= 4.656, p=.017^\ddagger$
160–180ms		$F(4,56)= 8.906, p=.002^\ddagger$	$F(4,56)= 21.102, p<.001^\dagger$	$F(4,56)= 30.012, p<.001^\dagger$	$F(4,56)= 25.302, p<.001^\dagger$	$F(4,56)= 10.062, p<.001^\ddagger$

Individual Subject Analysis. Results from randomization tests comparing the VEP at the central occipital site and two lateral sites for the 2550ms condition against all other ISIs, for the three time periods of interest. Individual-level VEP modulation is seen in all participants in the 160–180ms time period when comparing the most disparate ISIs for the central site and one lateral site.

Table 3

3A. Central occipital site (Oz)				
No. of subjects out of 15 (Average minimum no. of sweeps required $\pm$ Standard Deviation)				
2550 vs.	200	300	550	1050
90–110ms	7 (66 $\pm$ 26)	8 (90 $\pm$ 58)	8 (93 $\pm$ 50)	3 (93.3 $\pm$ 31)
130–150ms	15 (56 $\pm$ 27)	13 (57 $\pm$ 33)	13 (48 $\pm$ 14)	10 (60 $\pm$ 28)
160–180ms	15 (57 $\pm$ 27)	15 (58 $\pm$ 35)	14 (49 $\pm$ 20)	14 (69 $\pm$ 40)
3B. Right lateral site (O2)				
No. of subjects out of 15 (Average minimum no. of sweeps required $\pm$ Standard Deviation)				
2550 vs.	200	300	550	1050
90–110ms	8 (98 $\pm$ 61)	10 (114 $\pm$ 55)	12 (105 $\pm$ 58)	6 (136 $\pm$ 66)
130–150ms	14 (50 $\pm$ 16)	13 (50 $\pm$ 14)	13 (62 $\pm$ 44)	12 (76 $\pm$ 30)
160–180ms	15 (66 $\pm$ 34)	15 (66 $\pm$ 24)	14 (56 $\pm$ 17)	11 (90 $\pm$ 42)
3C. Left lateral site (O1)				
No. of subjects out of 15 (Average minimum no. of sweeps required $\pm$ Standard Deviation)				
2550 vs.	200	300	550	1050
90–110ms	9 (72 $\pm$ 29)	9 (79 $\pm$ 34)	9 (95 $\pm$ 46)	8 (127.6 $\pm$ 54)
130–150ms	13 (65 $\pm$ 41)	13 (69 $\pm$ 53)	13 (53 $\pm$ 19)	12 (75 $\pm$ 41)
160–180ms	13 (68 $\pm$ 34)	13 (58 $\pm$ 19)	13 (55 $\pm$ 14)	10 (92 $\pm$ 54)