Measuring contrast processing in the visual system using SSVEP

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Review for Vis Neurosci

Abstract:

Contrast is the currency of the early visual system. Measuring the way that the computations underlying contrast processing depend on factors such as spatial and temporal frequency, age, clinical conditions, eccentricity, chromaticity and the presence of other stimuli has been a focus of vision science for at least 100 years. One of the most productive experimental approaches in this field has been the use of the 'steady-state visually-evoked potential' (SSVEP): a technique where contrast modulating inputs are 'frequency tagged' (presented at well-defined frequencies and phases) and the electrical signals that they generate in the brain are analyzed in the temporal frequency domain. SSVEPs have several advantages over conventional measures of visually-evoked responses: they have relatively unambiguous ouput measures, a high SNR, and they allow us to analyze interactions between stimulus components using a convenient mathematical framework. Here we describe how SSVEPs have been used to study visual contrast over the past 70 years (Dawson, 1954). Because our thinking about SSVEPs is well-described by simple mathematical models, we embed code that illustrates key steps in the modelling and analysis. This paper can therefore be used both as a review of the use of SSVEP in measuring human contrast processing, and as an interactive learning aid.

Introduction

Neurons in the visual areas of the brain are primarily responsive to changes in cone photoreceptor activations across time and space. This property, referred to as contrast, sets the fundamental limits of our visual abilities, which remain steady over a remarkably wide range

of environmental light levels. The human response to contrast can be studied using many different techniques. Early work used psychophysical methods to measure contrast sensitivity (Campbell & Green, 1965), defined as the inverse of the lowest contrast that can be reliably detected. But neural responses can also be measured more directly using techniques such as fMRI, MEG, and EEG. Here we will describe how an EEG method known as the steady state visually evoked potential (SSVEP) technique has contributed to our understanding of human contrast processing in health, disease and throughout development.

The SSVEP is a continuous electrical response evoked in the brain by visual stimuli flickering at a constant frequency (Regan, 1966). For contrast-defined stimuli, such as sine-wave gratings, it is strongest at the occipital pole, adjacent to the early visual areas that generate the signal, although careful analysis of individual VEPs reveals multiple generators throughout visual cortex (Di Russo *et al.*, 2005, 2007). The flickering stimulus entrains neural population responses at multiples of the stimulus frequency, so continuous EEG data are typically analysed by taking the Fourier transform, and estimating the amplitude at these frequencies. Two common variants involve sinusoidal on-off flicker, where the stimulus alternates between a blank background and the peak contrast, and sinusoidal counterphase flicker, where the stimulus alternates in phase (i.e the black regions become white and the white regions become black). On-off flicker can drive independent populations of on- and off-cells in the retina once per cycle and can therefore produce a response at the fundamental flicker frequency, known as 1F, and its integer harmonics: 2F, 3F, 4F and so on. Counterphase flicker contains two transients per cycle and therefore does not produce a response at 1F, only at its even harmonics: 2F, 4F, 6F and so on. Because square-waves are spectrally broad-band, square wave flicker tends to produce more complex spectral harmonics than sine-wave flicker.

The higher harmonics of the steady-state signal are generally thought to reflect nonlinear processing in the visual system (Regan & Regan, 1988). SSVEP signals can also be elicited by periodic changes of stimulus properties other than achromatic and chromatic contrast, such as motion, stereo depth, and facial identity or expression (see Norcia *et al.*, 2015, for an overview); however our focus here is on the contrast response.

Why measure responses to contrast?

Contrast is one of the most fundamental pieces of information that the eye transmits to the brain. It can be defined as the change in cone photoreceptor activity over space ('spatial contrast') or time ('temporal contrast'). Cone photoreceptors - which drive precortical opponent pathways - contribute to both chromatic and achromatic contrast, and although most of the research we describe here focuses on achromatic contrast, SSVEPs have proven to be an excellent measure of early chromatic processing as well (McKeefry *et al.*, 1996; Baseler & Sutter, 1997; Di Russo *et al.*, 2001).

Contrast is relatively simple to define: typically, it is specified as the percentage deviation of a uniform stimulus from the background. So, for example, a disk of 100 units of cone

activation (I_{stim}) surrounded by a 'background' of 50 units of activation ($I_{\text{background}}$) has a contrast of $\frac{I_{\text{stim}}-I_{\text{background}}}{I_{\text{background}}} = 100\%$. Where patterns are more complex (for example, the sine-wave gratings or Gabor patches common in vision science), the Michelson (1927) definition of contrast is specified by the maximum and minimum excursions from the mean:

$$\frac{I_{\text{stimmax}} - I_{\text{stimmin}}}{I_{\text{stimmax}} + I_{\text{stimmin}}}. \tag{1}$$

These contrast definitions are appropriate both to photometric measures of stimulus contrast (for example, luminance; Lennie *et al.* (1993)) and also to definitions based on cone excitations (MacLeod & Boynton, 1979; Derrington *et al.*, 1984) which are more common in work on chromatic processing.

Although its mathematical definition is straightforward, the computations that underlie contrast processing in the brain have been the subject of intense research for many decades. The neural code for contrast, even in the earliest parts of visual cortex, is not simply a linear transform of the contrast at the retina - instead, contrast signals undergo a cascade of nonlinear processing stages that, broadly, attempt to normalise the output relative to the spatiotemporal environment. This normalization, achieved through a computation called 'contrast gain control' (Heeger, 1992; Foley, 1994; Carandini & Heeger, 2011) maximises the sensitivity of the visual system by making optimal use of neuronal bandwidth. As an example, a grating placed at the centre of a low-contrast background typically appears more intense than the same grating when superimposed on a high contrast background (see Figure 1).

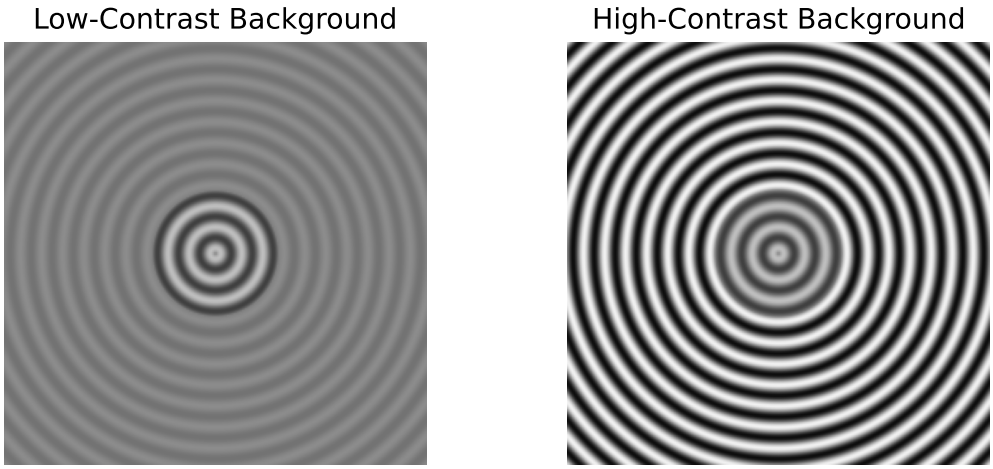

Figure 1: The perceived contrast of a stimulus depends on its context. A high contrast surround reduces the apparent contrast of the central 'probe' region.

A significant body of research into contrast processing is concerned with how these normalization mechanisms depend on colour (Chen *et al.*, 2000), orientation (Foley, 1994), eye of origin (Legge, 1979; Baker *et al.*, 2007), spatial and temporal frequency (Meese & Baker, 2009), location (Polat & Sagi, 1993; Tadin *et al.*, 2003; Petrov *et al.*, 2005), age (Betts *et al.*, 2005), and the presence of neurological disorders (Porciatti *et al.*, 2000; Tsai *et al.*, 2011). The SSVEP has proven to be invaluable in this research because it provides an objective readout of contrast representation at different stages of the visual system, and allows us to 'tag' the probe and background at separate frequencies.

Because it provides a direct read-out of neural population activity, the SSVEP signal can reveal key features of neural signal transduction. For example, by varying the peak stimulus contrast parametrically, a 'contrast vs response' function can be measured - where the 'response' is typically defined as the amplitude of the SSVEP frequency component at the stimulus frequency, or a low multiple thereof. This corresponds closely to similar functions reported by studies measuring single unit activity or local field potentials in the cortex (Shapley & Victor, 1980; Morrone *et al.*, 1982). However the SSVEP has the advantage that it is non-invasive, and so can be measured in awake, behaving human participants.

To understand the utility of the contrast SSVEP, it is helpful to identify the cascade of processing stages in the early visual system that give rise to it. In the following section we illustrate how a typical SSVEP signal measured over early visual cortex might contain information about a large number of early visual computations.

Contrast processing - linear and nonlinear

Neurons have a limited dynamic range, yet they can transmit information about visual stimuli that span many orders of magnitude. In the domain of contrast, to some extent this is accomplished at a population level - individual neurons typically implement a non-linear, sigmoidal contrast vs response (CRF) transducer (Tolhurst *et al.*, 1981; Albrecht & Hamilton, 1982) and different neurons exhibit peak sensitivity (defined as the maximum slope of the function) at different contrast levels (Carandini & Heeger, 1994; Carandini *et al.*, 1998; Busse *et al.*, 2009). A neuronal population will therefore span a sensitivity range greater than any individual member.

Individual neurons at multiple stages of the visual hierarchy also change their sensitivity depending on the average spatiotemporal contrast energy of their environment. This "normalisation" process is dynamic and nonlinear and is well-modeled by a hyperbolic ratio function in which the response of each neuron is modulated by a local 'gain pool' composed of the summed responses of the local neuronal population (Heeger, 1992; Busse *et al.*, 2009; Carandini & Heeger, 2011; Baker & Wade, 2017).

To better understand these processes, we will show how sinusoidal input signals might be processed by the visual system to produce SSVEPs. Figure 2 illustrates how sine waves of

different contrasts are processed in a linear system. The first panel shows the input sine wave, which would be used to modulate stimulus amplitude over time. Notice that there are five peaks in the waveform during the one second sample, so the stimulation frequency is 5Hz (F1). The second panel shows Fourier transform of the waveform, which contains a substantial peak at this frequency. If we parametrically vary the stimulus contrast (i.e. the amplitude of the waveform), the amplitude of the F1 component increases linearly with contrast (right panel).

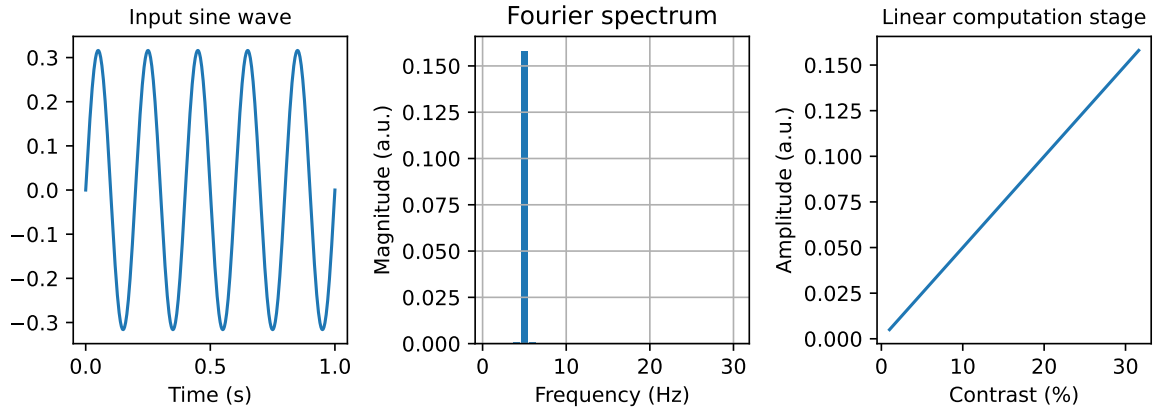

Figure 2: Illustration of a sinusoidal input signal (left), its Fourier spectrum (middle), and how the amplitude of the first harmonic component increases with contrast (right). These calculations assume an entirely linear system.

Next we can consider the impact of a nonlinearity in processing on the responses. One of the simplest nonlinearities is the function that describes a cell's response to different levels of contrast. In Figure 3 this is modeled by a hyperbolic ratio function resulting in a saturating non-linearity:

$$R_{\max} = \frac{C_{\text{in}}^n}{C_{50}^n + C_{\text{in}}^n}, \tag{2}$$

where $R_{\max}$ describes the maximum response level, C_{in} is the input contrast (or the time-varying waveform), C_{50} is the 'semi-saturation constant' (the point at which the response is at half-maximum) and n controls the steepness of the curve.

This nonlinearity has clear effects on signal transduction. The sinusoidal waveform is distorted by the nonlinearity, and appears frequency doubled (left panel of Figure 3; note that other nonlinearities such as rectification and squaring can have similar effects). The distortion is reflected in the Fourier spectrum (middle panel of Figure 3), which now includes responses at integer multiples (known as harmonics) of the stimulation frequency (10, 20 and 30Hz), but no response at the fundamental (5Hz). Finally, the contrast response function is now nonlinear (right panel of Figure 3). Although the hyperbolic ratio function (Equation 2) is monotonic,

the CRF resulting from measuring the amplitude of the second harmonic (2F) component contains a slight roll-off at high input contrasts. This results from the distortion of the input sine waves at high contrast due to a combination of the full-wave rectification and saturating non-linearity. Power at other harmonics increases, and the total power generated by the input is monotonic. This roll-off is often seen in experimental data and has been referred to as 'supersaturation' (Tyler & Apkarian, 1985; Peirce, 2007).

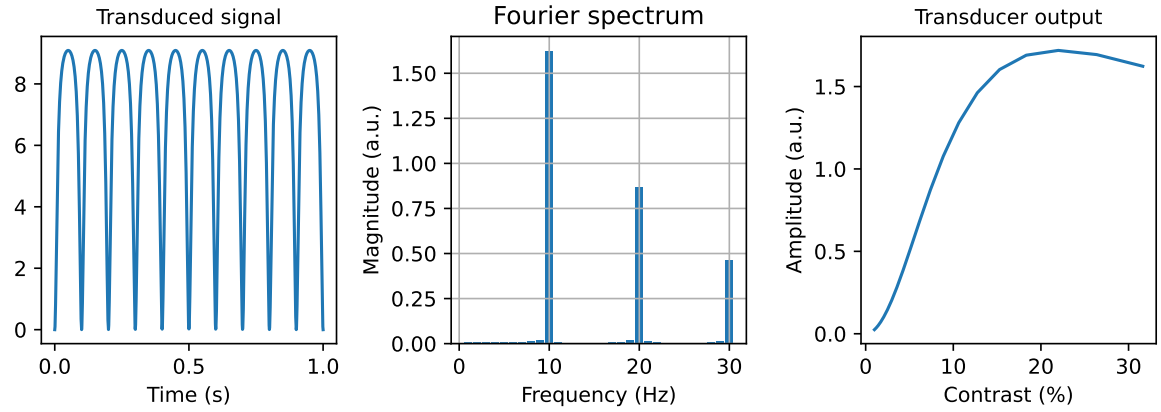

Figure 3: Illustration of how a sinusoidal input signal is affected by a nonlinear transducer. The input wavefore (left panel) is frequency doubled by the squaring operator, and now features energy at the second harmonic (10Hz) and its multiple (middle panel). The contrast response function is now nonlinear, and saturates at high contrasts (right panel).

To illustrate the effect of contrast gain control (Heeger, 1992), we next include a second component (a 'mask') that contributes to the gain pool of the first (the 'target'). The mask stimulus will suppress the response at the target frequency, reducing its amplitude. The suppression is reciprocal - activity at the mask frequency is also reduced by the presence of the target, in a contrast-dependent manner (Busse *et al.*, 2009). At a single pair of (matched) contrast levels, we see a complex pattern of intermodulation terms in the transduced waveforms (left panel of Figure 4) and in the Fourier spectrum (middle panel of Figure 4). The two components interact generating nonlinear intermodulation terms at sums and differences of the input frequencies (F1, F2). The nature of the interaction — and therefore the pattern of intermodulation terms — is determined by the computations happening as the contrast signal moves from retina to cortex (Regan & Regan, 1988).

If the two inputs were simply added together, the representation of the resulting signal in the Fourier domain would be the linear sum of the two independent signals (i.e. peaks at F1 and F2). However, it is important to take physiology into account. Contrast gain control reduces the amplitude of the responses via a suppressive process, which can be incorporated into our transducer function via an additional denominator term:

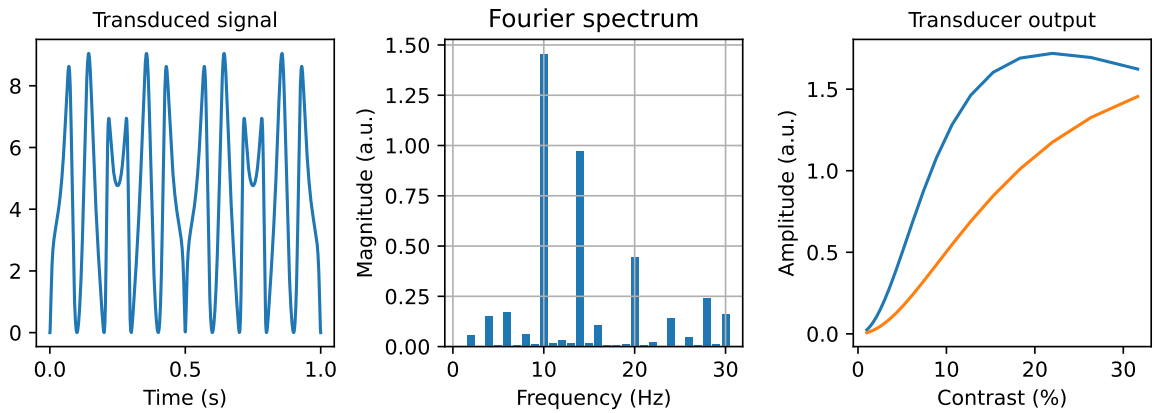

Figure 4: Demonstration of how two inputs of different frequencies are processed by a nonlinear transducer. Additional harmonics are apparent in the Fourier spectrum (middle panel), and the contrast response function is suppressed (right panel).

$$R_{\max} = \frac{C_{\text{in}}^n}{C_{50}^n + C_{\text{in}}^n + C_{\text{mask}}^n}, \tag{3}$$

where C_{mask} reflects the contrast of the mask component at a distinct frequency from that of the target. The effect of this extra term is to reduce the target response (see right panel of Figure 4). For a linear contrast axis, the contrast response function becomes shallower, whereas on a logarithmic contrast axis it maintains its steepness and shifts to the right. Suppressive effects of this kind have been obtained using SSVEP with a variety of different types of mask, including orthogonal overlaid masks, surround masks, and dichoptic masks (for a meta-analysis see Baker *et al.*, 2021).

Even without considering a spatial component, the early visual system is far more complex than the model here suggests. For example as well as cells that code positive or negative contrast in a more or less continuous manner, the retina also contains 'transient' cells that code temporal changes in contrast. These cells (Kuffler *et al.*, 1957; Alpern, 1971), and cells with similar properties in the LGN (Levitt *et al.*, 2001) and cortex (Hubel & Wiesel, 1959; Movshon, 1975), will introduce second harmonic components even when the stimulus itself is modulated in an on-off fashion. Analogously, in the spatial domain, so-called 'simple cells' are sensitive to the polarity of a spatial contrast modulation while 'complex cells' respond to the presence of patterned spatial contrast irrespective of its spatial position (Hubel & Wiesel, 1962). The SSVEP response to a contrast-reversing sine-wave grating therefore contains information about nonlinear computations performed across a range of retinal and cortical cell types.

The complexity of even a simple simulation of the frequency-domain signal arising from nonlinear interactions is intriguing. Presumably, the signal measured from early visual cortex

is the result of a cascade of nonlinear retinal and cortical operations up to that point. It therefore contains a 'signature' of the computational nature, order and parameters of those operations - including the shape of the transducer functions and the computations involved in signal combination. In principle, that information could be recovered from the SSVEP signal - a possibility recognised in the early days of the technique (Regan & Regan, 1988). Although characterising the complete set of computations along entire processing pathway is challenging, careful parametric variation of the input stimuli does allow us to fit models of early visual gain control using SSVEP data. For example, Tsai *et al.* (2012) demonstrated that a gain control model gave a good account of the pattern of intermodulation responses produced by two overlaid patterns flickering at different frequencies. This was achieved by passing full stimulus waveforms through the transducer nonlinearity, and calculating the Fourier spectrum of the model output. Our own work on signal combination across eyes and space similarly demonstrated close correspondence between the predictions of a computational model and empirical data in humans (Baker & Wade, 2017). More detailed modelling of intracortical recordings (Groen *et al.*, 2022) has revealed details of the timecourse of gain control effects, specifically that normalization is delayed slightly relative to the initial visual response.

Similar changes to the contrast response function might also be obtained using adaptation paradigms, in which the visual system is exposed to high contrast stimuli for long durations. Psychophysically, adaptation increases detection thresholds, but has little effect on contrast discrimination performance (Ross *et al.*, 1993), much like pattern masks (Foley, 1994). Although SSVEP adaptation effects show strong tuning for orientation (Campbell & Maffei, 1970; Vergeer *et al.*, 2018) and spatial frequency (Mecacci & Spinelli, 1976), there appear to be no studies measuring the full SSVEP contrast response function before and after an extended period of adaptation.

Measuring the development of contrast processing

An early use of the SSVEP was to provide an objective estimate of spatial contrast sensitivity in infants, without requiring behavioural responses. In well-motivated adults, psychophysical measurements of contrast sensitivity remain the gold standard. However, it is difficult and time consuming to obtain reliable psychophysical data from infants. In these cases, SSVEP measurements represent a fast and efficient method for measuring low-level visual responses (Tyler *et al.*, 1979; Braddick *et al.*, 1986; Norcia *et al.*, 1990) and the high SNR of SSVEP means that infants need only look at the screen for short periods of time.

Because SSVEP responses at detection threshold are very small, estimating a threshold is achieved by measuring the contrast response function at relatively high levels, and extrapolating back along the function (either contrast vs response measured at a constant spatial frequency or spatial frequency vs response at a constant contrast level) to estimate its intercept with the x-axis (see Figure 5). This contrast level was shown to correspond approximately with psychophysically measured detection thresholds (Norcia *et al.*, 1986).

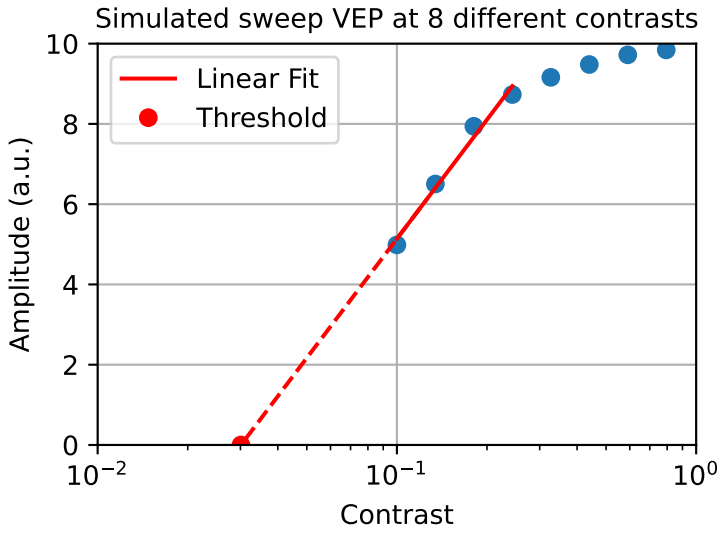

Figure 5: Sweep VEP simulation showing how a contrast detection threshold can be estimated from sweep VEP data measured at higher contrasts. The solid line is the regression fit to the lowest four data points, and the dashed line extrapolates the fit back to determine the contrast value when y=0, which gives a threshold estimate (red point).

A robust estimate of the threshold therefore requires the measurement of the SSVEP amplitude at many different super-threshold contrasr levels. This was made faster by the development of the 'sweep VEP' paradigm in which the stimulus changed its contrast, spatial frequency or some other property, throughout a trial (Tyler *et al.*, 1979). To avoid hysteresis effects, the sweep is sometimes conducted both up and down in the same experiment Norcia & Tyler (1985*a*). The sweep VEP (really, a sweep 'SSVEP') technique is now commonly-used to obtain a rapid and objective measurement of visual acuity. In particular, because of its relative speed and simplicity, this technique has now become a standard for conducting tests of visual acuity in very young subjects or where behavioural tests are not appropriate (Ridder, 2004; Bach *et al.*, 2008; Hoffmann *et al.*, 2017; Bach & Farmer, 2020).

This approach has revealed much about the development of visual abilities in infants (Harris *et al.*, 1976; Atkinson *et al.*, 1979; Braddick *et al.*, 1986). In general, SSVEP measurements of infant vision have revealed that contrast sensitivity for both achromatic and chromatic contrast as well as stereoscopic depth perception develops earlier than had been supposed previously based on behavioural readouts (Dobson *et al.*, 1978; Norcia & Tyler, 1985*b*) with both chromatic and achromatic contrast detection reaching near-adult levels by around six months. Spatial acuity as measured by SSVEP reaches adult levels more slowly, but near-adult levels are recorded around one year (Norcia & Tyler, 1985*b*; Hamer *et al.*, 1989) compared to around six to seven years with behavioural measures (Atkinson & Braddick, 1983; Ellemberg *et al.*, 1999). At least some of this difference is likely due to the relative objectivity and high

SNR of the SSVEP technique compared to other methods such as preferential looking, which require careful measurement of the infant's gaze direction. However it should be noted that other groups have reported electrophysiological correlates of visual acuity that more closely match the behavioural measures (De Vries-Khoe & Spekreijse, 1982).

The SSVEP technique has also been used to study the development of the contrast gain control mechanisms described in the previous section (Candy *et al.*, 2001; Pei *et al.*, 2017). Although contrast gain control is measurable in infants as young as six weeks old (Morrone & Burr, 1986; Skoczenski & Norcia, 1998; Candy *et al.*, 2001), its development appears to be slower, with adult levels being reached at approximately 11 years (Pei *et al.*, 2017).

Contrast processing in clinical conditions

The SSVEP technique has also been used to study clinical conditions, such as diseases and developmental disorders. This can often be informative regarding the underlying mechanism that characterises the condition. Here we focus on four conditions, but there is potential to apply the method more broadly, either as a diagnostic technique, or to monitor disease severity and progression, or the efficacy of treatments.

Epilepsy is a neurological condition in which patients experience seizures - episodes of uncontrolled neural activity that can cause unconsciousness, involuntary movements and convulsions, and atypical sensory experiences. Porciatti *et al.* (2000) showed that individuals with photosensitive epilepsy generate larger steady-state signals in response to flickering visual stimuli, and their contrast response functions saturate less than those of healthy controls. This is consistent with the idea that epilepsy involves a cortical hyperexciteability that makes seizures more likely. It is also the case for individuals with idiopathic generalised epilepsy (Tsai *et al.*, 2011), a subtype of epilepsy that has a less obvious link to vision. The differences apply across the whole contrast-response function, and so resemble a response gain effect (see Figure 6a), which might be due to reduced inhibition from neighbouring neurons. Differences in SSVEP amplitudes have also been reported in individuals with migraine (Shibata *et al.*, 2008), a condition also associated with cortical hyperexciteability.

Amblyopia is a disorder of binocular vision, characterised by one eye contributing much less to perception than the other. This is often due to strabismus (squint) or anisometropia (difference in optical prescription between the eyes) during development. Contemporary accounts suggest that the amblyopic eye is suppressed by signals from the fellow eye. SSVEPs provide a convenient and objective method to characterise the difference in neural response to signals in each eye, and typically show reduced responses to stimuli in the amblyopic eye (see Figure 6b) across the contrast range (Baker *et al.*, 2015; Lygo *et al.*, 2021). There are currently many novel binocular treatments for amblyopia under development, often involving virtual reality or stereo display systems designed to encourage the two eyes to work together. The steady-state approach may be more sensitive and objective than typical acuity measurements, and also has

the potential to measure suppression between the eyes directly (e.g. Zheng *et al.*, 2019; Hu *et al.*, 2023; Du *et al.*, 2023).

Autism is a condition often associated with differences in vision (Simmons *et al.*, 2009) and other senses (MacLennan *et al.*, 2022). Pei *et al.* (2014) used a sweep-VEP method with counterphase flickering stimuli, and found weaker responses in autistic children at spatial frequencies around 8c/deg, compared with age-matched controls. This was subsequently replicated in a further pediatric sample by Vilidaite *et al.* (2018) (see Figure 6c), who additionally found weaker responses in autistic adults at the second harmonic (using on/off flicker). Interestingly this study replicated its key findings in a *Drosophila* genetic model of autism (*Nhe3* mutations), illustrating the translational potential of the steady-state approach, as well as identifying a possible biomarker for autism.

Recent work on understanding Parkinson's disease has also used *Drosophila* genetic models. Afsari *et al.* (2014) found that mutant flies produced stronger SSVEP responses to flickering lights than control flies (see Figure 6d). The authors theorised that differences in early gain control during development might lead to visual deficits later in life. Although visual responses are a convenient assay of neural function, it is likely that same general process applies throughout the whole brain, including in the motor system where the core Parkinson's symptoms (tremor, rigidity, slow movement) manifest. The SSVEP differences were reduced by a kinase inhibitor that targets the dopamine system, demonstrating how model organisms can be used to test new pharmacological treatments. SSVEP responses also provide a potential method to diagnose Parkinson's before any symptoms manifest, and to monitor the effect of treatments.

Brain-computer interfaces

One widespread application of the SSVEP technique is in the design of brain-computer interfaces, which seek to control some aspect of a computer using neural signals. The high SNR and good frequency resolution of SSVEPs make them an ideal candidate for this approach. Typical studies involve presenting an array of stimuli at different flicker frequencies, and having the participant select one either by overt attention (i.e. shifting fixation to foveate the selected stimulus) or covert attention (i.e. deploying attention to one stimulus whilst keeping fixated). EEG signals are highly sensitive to both visual field position (Ales *et al.*, 2010) and attentional state (Lauritzen *et al.*, 2010; Verghese *et al.*, 2012), so the response to the selected stimulus will typically increase relative to the others, allowing it to be identified by an on-line algorithm.

Probably a summary of BCIs here.

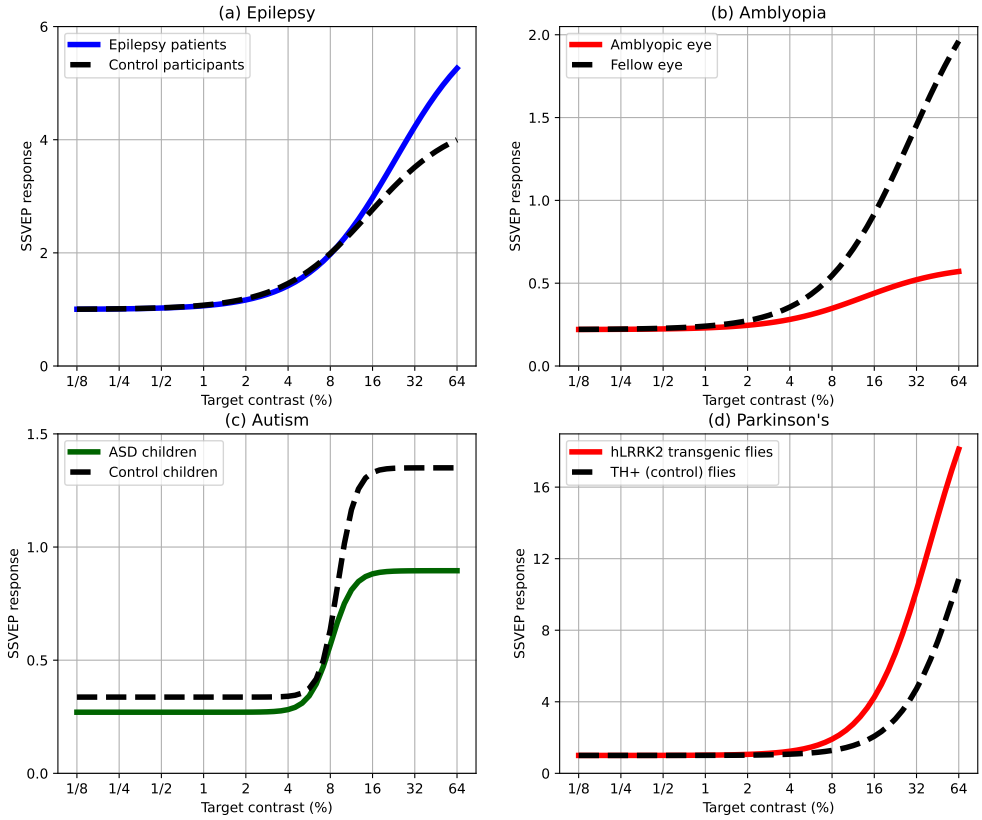

Figure 6: Example contrast response functions for different clinical conditions. Panel (a) shows modelled contrast response functions for epilepsy patients (blue) and control participants (black), based on the data of Tsai et al. (2011). Panel (b) shows functions for the amblyopic (red) and fellow (black) eyes of adults with amblyopia, based on the data of Baker et al. (2015). Panel (c) shows functions for children with (green) and without (black) a diagnosis of autism, based on the data of Vilidaite et al. (2018). Panel (d) shows data from *Drosophila melanogaster* (fruit flies) from Afsari et al. (2014). One day-old flies expressing a human gene linked to Parkinson's (hLRRK-G2019S) show increased SSVEP response amplitude and sensitivity (red) compared to control animals (black).

Conclusions

2: Sweeps and CRFs. Measurements of contrast sensitivity, extrapolating the sweep to zero response to get t'hold. Infants and adults?

3: Measurements of modulation. Figures adapted from other papers: Attention to space, attention to features, adaptation (?). masking/surround suppression

4: Clinical (Porciatti / Tsai/ Marmite/ Amblyopia / PD?)

5: Future directions (decoding in frequency domain?, animals? BCI?)

History

1. The basics of SSVEP and contrast sensitivity including a history of both fields

SSVEP (Steady-State Visual Evoked Potential): A continuous electrical response evoked in the brain by visual stimuli flickering at a constant frequency (Regan, 1966).

Contrast Sensitivity: The ability to detect differences in luminance between an object and its background (Campbell & Green, 1965).

Regan, D. (1966). Some characteristics of average steady-state and transient responses evoked by modulated light. Electroencephalography and clinical neurophysiology, 20(3), 238-248.

Campbell, F. W., & Green, D. G. (1965). Optical and retinal factors affecting visual resolution. J Physiology, 181, 576-593.

Check Regan paper for earlier (e.g. EEG refs). Norcia review will be helpful!

(From Tyler / Levi / Apkarian paper):

6. Regan, D.: Rapid methods for refracting the eye and assessing the visual acuity in amblyopia using steady-state visual evoked potentials. In Desmedt, J.E., editor: Visual Evoked Potentials in Man: New Developments, Oxford, 1977, Clarendon Press, pp. 418-426.

7. Fricker, S.J.: Narrow-band filter techniques for the detection and measurement of evoked responses, Electroencephalogr. Clin. Neurophysiol. 14:411, 1962.

8. Van der Tweel, L. H., Sem-Jacobsen, C.W., Kamp, A., Van Leeuwen, W.S., and Verings, F.T.H.: Objective determination of response to modulated light, Acta Physiol. Pharmacol. Neerl. 7:528, 1958.

9. Regan, D.: Latencies of evoked potentials to flicker and to pattern speedily estimated by simultaneous stimulation method, Electroencephalogr. Clin. Neurophysiol. 40:654, 1976.

10. Tyler, C.W., Apkarian, P., and Nakayama, K.: Multiple spatial frequency tuning of electrical responses from the human.…

[Around here perhaps a section about what gain control is, mentioning other methods as well including psychophysics, MRI, electrophysiology, and other EEG markers including ERPs

and evoked gamma band oscillations. Maybe outline the Heeger gain control model and its cousins.]

[Sure. But in fact gain control is only a small part of this story - especially in the early days. They were, I think, more interested in using SSVEP to measure absolute contrast sensitivity and to get lower bounds on things like infant visual development. Gain control might be better as a separate section later.]

2. Spatial, temporal frequency and contrast sensitivity measurements

Basically using SSVEP to measure a cortical output amplitude for any given input contrast. You can vary parameters like SF, TF, position, color and of course contrast. Early on people realised that you can 'sweep' the stimulus to get a CRF. You broadly get a line in log contrast space if you do that (Tyler) - then you can extrapolate that line down to zero response to estimate the threshold. That doesn't >quite< work but it's pretty close.

You can also use this for 'difficult' populations like babies. One interesting story was about how SSVEP become a replacement for preferential looking (which was the other way of looking at infant visual development). See e.g. Davida Teller. SSVEPs allowed people to make objective measurements of contrast sensitivity development and deduce that the visual system was more mature (e.g. more functional) in infancy than previously expected. Also measures of colour sensitivity. Tinyeyes is based off those measurements. Other people: Tyler, Norcia, Gunilla H-P, many of the people at SKERI in the 1980s and 90s. Norcia 86,88,90 - mentioned in Regan's nice autobiography :

In parallel of course, people were using frequency tagging to do single unit work - the 1F vs 2F simple/complex cell classification scheme was all about this (Lennie and others).

3. SSVEP in functional localization

Techniques like fMRI have been combined with SSVEP to achieve more precise spatial localization (Di Russo et al., 2007). See however the Ales cruciform paper.

Ales and Norcia:... (showed that people's intuition about V1 upper / lower v.f reversing polarity wasn't really correct). This feels a little outside our scope though... We have also combined SSVEP with source imaging techniques to probe responses in different cortical locations (again, Ales papers, some early stuff from Stan K? Appelbaum, Wade, Norcia figure/ground...) and then a host of later work from that lab and others.

4. SSVEP and contrast gain control including adaptation, masking, and attention

[The story goes: Up to the lte 90s people were primarily interested in measuring contrast sensitivity - the shape of the response function was assumed to be basically log-linear - and they fit it with straight lines to extrapolate back to zero response. But then (once Heeger's 1992 paper had sunk in - see also stuff like Shapley and Victor 1981 (Shapley & Victor, 1981)), people started thinking about gain control - Candy and Norcia in about 1999, Porciatti, probably a load of Tyler papers that I don't even know about...]. Probably look in p

And then people worked out that if you can use SSVEP to measure contrast responses, you can also use it to measure things that modulate contrast responses. These include adaptation, masking, suppression, attention (feature and space), clinical things.

Adaptation:

Continuous exposure to high-contrast patterns reduces contrast sensitivity, which can be measured using SSVEP (Ross et al., 1989). Others? Baker recent gain control paper is perhaps worth mentioning here as a 'confound' of sorts. Engel 2018 *(Vergeer et al., 2018)*. This paper is interesting *(Rideaux et al., 2023)* and >sort< of SSVEP.

Masking:

High contrast masks can suppress the visibility of low contrast patterns, which has implications in SSVEP amplitude (Haynes et al., 2003).

Attention: Directing attention can enhance contrast sensitivity, as shown in studies using SSVEP (Müller et al., 2006). Also Tsai (dynamics), Baker / Wade (several), Winawer? I think JW has a nice dynamic model of normalization with some MEG data. Busse et al cat/human comparison. Candy and Norcia 2001 JNS (Candy et al., 2001)

Ross, J., Speed, H. D., & Morgan, M. J. (1989). The effects of adaptation and masking on incremental thresholds for contrast. Vision research, 29(2), 205-215.

Haynes, J. D., Roth, G., Stadler, M., & Heinze, H. J. (2003). Neuromagnetic correlates of perceived contrast in primary visual cortex. Journal of Neurophysiology, 89(6), 2655-2666.

Müller, M. M., Picton, T. W., Valdes-Sosa, P., Riera, J., Teder-Sälejärvi, W. A., & Hillyard, S. A. (2006). Effects of spatial selective attention on the steady-state visual evoked potential in the 20–28 Hz range. Cognitive Brain Research, 24(1), 1-13.

5. Clinical implications

Clinical applications (this is a whole section)

Not sure exactly how SSVEP used in clinic. mfVEP?

, e.g., in monitoring visual impairments, tracking neuronal diseases, or neurofeedback (Norcia et al., 2015).

Tsai epilepsy (Tsai et al., 2011). Other photosensitive epilepsy: Porciatti (Porciatti et al., 2000)

Citation:

Migraine (Regan et al). Autism?

Norcia, A. M., Appelbaum, L. G., Ales, J. M., Cottereau, B. R., & Rossion, B. (2015). The steady-state visual evoked potential in vision research: A review. Journal of vision, 15(6), 4-4.

Animal work: Flies (Eliott, West, Himmelberg, Ales, Norcia): Mice/rats (probably many - can't think off the top of my head - we were working with a mouse EEG person at UCSF about 12 years ago...), Monkeys (Kiorpes?),

6. Future directions

Use as a readout of modulations. TMS? FUS? Marmite B12 / Fluoxetine / amblyopia in Rats,

GABA Huang

There is a lot of SSVEP interest these days because of BCIs. I think it's pretty weak but there is >so much< of it that it might be worth mentioning...

Advanced signal processing techniques and machine learning can be integrated to improve SSVEP-based systems (Zhu et al., 2010).

Exploring new clinical and diagnostic applications, understanding neurological diseases, and developing novel therapeutic interventions.

Citation:

Zhu, D., Bieger, J., Molina, G. G., & Aarts, R. M. (2010). A survey of stimulation methods used in SSVEP-based BCIs. Computational intelligence and neuroscience, 2010.

References

Afsari F, Christensen KV, Smith GP, Hentzer M, Nippe OM, Elliott CJH & Wade AR (2014). Abnormal visual gain control in a Parkinson's disease model. *Human Molecular Genetics* **23,** 4465–4478.

Albrecht DG & Hamilton DB (1982). Striate cortex of monkey and cat: Contrast response function. *J Neurophysiol* **48,** 217–237.

Ales JM, Yates JL & Norcia AM (2010). V1 is not uniquely identified by polarity reversals of responses to upper and lower visual field stimuli. *Neuroimage* **52,** 1401–1409.

Alpern M (1971). Rhodopsin kinetics in the human eye. *J Physiol* **217,** 447–471.

Atkinson J & Braddick O (1983). Assessment of visual acuity in infancy and early childhood. *Acta Ophthalmol Suppl* **157,** 18–26.

Atkinson J, Braddick O & French J (1979). Contrast sensitivity of the human neonate measured by the visual evoked potential. *Invest Ophthalmol Vis Sci* **18,** 210–213.

Bach M & Farmer JD (2020). Evaluation of the "freiburg acuity VEP" on commercial equipment. *Doc Ophthalmol* **140,** 139–145.

Bach M, Maurer JP & Wolf ME (2008). Visual evoked potential-based acuity assessment in normal vision, artificially degraded vision, and in patients. *Br J Ophthalmol* **92,** 396–403.

Baker DH, Meese TS & Summers RJ (2007). Psychophysical evidence for two routes to suppression before binocular summation of signals in human vision. *Neuroscience* **146,** 435–448.

Baker DH, Simard M, Saint-Amour D & Hess RF (2015). Steady-state contrast response functions provide a sensitive and objective index of amblyopic deficits. *Invest Ophthalmol Vis Sci* **56,** 1208–1216.

Baker DH, Vilidaite G & Wade AR (2021). Steady-state measures of visual suppression. *PLoS computational biology* **17,** e1009507.

Baker DH & Wade AR (2017). Evidence for an Optimal Algorithm Underlying Signal Combination in Human Visual Cortex. *Cerebral Cortex (New York, NY: 1991)* **27,** 254–264.

Baseler HA & Sutter EE (1997). M and p components of the VEP and their visual field distribution. *Vision Res* **37,** 675–690.

Betts LR, Taylor CP, Sekuler AB & Bennett PJ (2005). Aging reduces center-surround antagonism in visual motion processing. *Neuron* **45,** 361–366.

Braddick OJ, Wattam-Bell J & Atkinson J (1986). Orientation-specific cortical responses develop in early infancy. *Nature* **320,** 617–619.

Busse L, Wade AR & Carandini M (2009). Representation of concurrent stimuli by population activity in visual cortex. *Neuron* **64,** 931–942.

Campbell FW & Green DG (1965). Optical and retinal factors affecting visual resolution. *J Physiol* **181,** 576–593.

Campbell FW & Maffei L (1970). Electrophysiological evidence for the existence of orientation and size detectors in the human visual system. *J Physiol* **207,** 635–652.

Candy TR, Skoczenski AM & Norcia AM (2001). Normalization models applied to orientation masking in the human infant. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* **21,** 4530–4541.

Carandini M & Heeger DJ (1994). Summation and division by neurons in primate visual cortex. *Science* **264,** 1333–1336.

Carandini M & Heeger DJ (2011). Normalization as a canonical neural computation. *Nat Rev Neurosci* **13,** 51–62.

Carandini M, Movshon JA & Ferster D (1998). Pattern adaptation and cross-orientation interactions in the primary visual cortex. *Neuropharmacology* **37,** 501–511.

Chen C, Foley JM & Brainard DH (2000). Detection of chromoluminance patterns on chromoluminance pedestals i: Threshold measurements. *Vision Res* **40,** 773–788.

Dawson GD (1954). A summation technique for the detection of small evoked potentials. *Electroencephalography and Clinical Neurophysiology* **6,** 65–84.

De Vries-Khoe L & Spekreijse H (1982). Maturation of luminance and pattern EPs in man. *Doc Ophthalmol Proc Ser* **31,** 461–475.

Derrington AM, Krauskopf J & Lennie P (1984). Chromatic mechanisms in lateral geniculate nucleus of macaque. *J Physiol* **357,** 241–265.

Di Russo F, Pitzalis S, Aprile T, Spitoni G, Patria F, Stella A, Spinelli D & Hillyard SA (2007). Spatiotemporal analysis of the cortical sources of the steady-state visual evoked potential. *Hum Brain Mapp* **28,** 323–334.

Di Russo F, Pitzalis S, Spitoni G, Aprile T, Patria F, Spinelli D & Hillyard SA (2005). Identification of the neural sources of the pattern-reversal VEP. *Neuroimage* **24,** 874–886.

Di Russo F, Spinelli D & Morrone MC (2001). Automatic gain control contrast mechanisms are modulated by attention in humans: Evidence from visual evoked potentials. *Vision*

Res **41,** 2435–2447.

Dobson V, Teller DY & Belgum J (1978). Visual acuity in human infants assessed with stationary stripes and phase-alternated checkerboards. *Vision Res* **18,** 1233–1238.

Du X, Liu L, Dong X & Bao M (2023). Effects of altered-reality training on interocular disinhibition in amblyopia. *Ann N Y Acad Sci* **1522,** 126–138.

Ellemberg D, Lewis TL, Liu CH & Maurer D (1999). Development of spatial and temporal vision during childhood. *Vision Res* **39,** 2325–2333.

Foley JM (1994). Human luminance pattern-vision mechanisms: Masking experiments require a new model. *J Opt Soc Am A Opt Image Sci Vis* **11,** 1710–1719.

Groen IIA, Piantoni G, Montenegro S, Flinker A, Devore S, Devinsky O, Doyle W, Dugan P, Friedman D, Ramsey NF, Petridou N & Winawer J (2022). Temporal dynamics of neural responses in human visual cortex. *J Neurosci* **42,** 7562–7580.

Hamer RD, Norcia AM, Tyler CW & Hsu-Winges C (1989). The development of monocular and binocular VEP acuity. *Vision Res* **29,** 397–408.

Harris L, Atkinson J & Braddick O (1976). Visual contrast sensitivity of a 6-month-old infant measured by the evoked potential. *Nature* **264,** 570–571.

Heeger DJ (1992). Normalization of cell responses in cat striate cortex. *Vis Neurosci* **9,** 181–197.

Hoffmann MB, Brands J, Behrens-Baumann W & Bach M (2017). VEP-based acuity assessment in low vision. *Doc Ophthalmol* **135,** 209–218.

Hu J, Chen J, Ku Y & Yu M (2023). Reduced interocular suppression after inverse patching in anisometropic amblyopia. *Front Neurosci* **17,** 1280436.

Hubel DH & Wiesel TN (1959). Receptive fields of single neurones in the cat's striate cortex. *J Physiol* **148,** 574–591.

Hubel DH & Wiesel TN (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol* **160,** 106–154.

Kuffler SW, Fitzhugh R & Barlow HB (1957). Maintained activity in the cat's retina in light and darkness. *J Gen Physiol* **40,** 683–702.

Lauritzen TZ, Ales JM & Wade AR (2010). The effects of visuospatial attention measured across visual cortex using source-imaged, steady-state EEG. *Journal of Vision* **10,** 39.

Legge GE (1979). Spatial frequency masking in human vision: Binocular interactions. *J Opt Soc Am* **69,** 838–847.

Lennie P, Pokorny J & Smith VC (1993). Luminance. *J Opt Soc Am A* **10,** 1283–1293.

Levitt JB, Schumer RA, Sherman SM, Spear PD & Movshon JA (2001). Visual response properties of neurons in the LGN of normally reared and visually deprived macaque monkeys. *J Neurophysiol* **85,** 2111–2129.

Lygo FA, Richard B, Wade AR, Morland AB & Baker DH (2021). Neural markers of suppression in impaired binocular vision. *NeuroImage* **230,** 117780.

MacLennan K, O'Brien S & Tavassoli T (2022). In our own words: The complex sensory experiences of autistic adults. *J Autism Dev Disord* **52,** 3061–3075.

MacLeod DI & Boynton RM (1979). Chromaticity diagram showing cone excitation by stimuli of equal luminance. *J Opt Soc Am* **69,** 1183–1186.

McKeefry DJ, Russell MH, Murray IJ & Kulikowski JJ (1996). Amplitude and phase variations

of harmonic components in human achromatic and chromatic visual evoked potentials. *Vis Neurosci* **13,** 639–653.

Mecacci L & Spinelli D (1976). The effects of spatial frequency adaptation on human evoked potentials. *Vision Research* **16,** 477–479.

Meese TS & Baker DH (2009). Cross-orientation masking is speed invariant between ocular pathways but speed dependent within them. *J Vis* **9,** 2.1–15.

Michelson A (1927). *Studies in optics*. University of Chicago Press.

Morrone MC & Burr DC (1986). Evidence for the existence and development of visual inhibition in humans. *Nature* **321,** 235–237.

Morrone MC, Burr DC & Maffei L (1982). Functional implications of cross-orientation inhibition of cortical visual cells. I. Neurophysiological evidence. *Proc R Soc Lond B Biol Sci* **216,** 335–354.

Movshon JA (1975). The velocity tuning of single units in cat striate cortex. *J Physiol* **249,** 445–468.

Norcia AM, Appelbaum LG, Ales JM, Cottereau BR & Rossion B (2015). The steady-state visual evoked potential in vision research: A review. *Journal of vision* **15,** 4–4.

Norcia AM & Tyler CW (1985*b*). Infant VEP acuity measurements: Analysis of individual differences and measurement error. *Electroencephalography and Clinical Neurophysiology* **61,** 359–369.

Norcia AM & Tyler CW (1985*a*). Spatial frequency sweep VEP: Visual acuity during the first year of life. *Vision Research* **25,** 1399–1408.

Norcia AM, Tyler CW & Allen D (1986). Electrophysiological assessment of contrast sensitivity in human infants. *Am J Optom Physiol Opt* **63,** 12–15.

Norcia AM, Tyler CW & Hamer RD (1990). Development of contrast sensitivity in the human infant. *Vision Res* **30,** 1475–1486.

Pei F, Baldassi S & Norcia AM (2014). Electrophysiological measures of low-level vision reveal spatial processing deficits and hemispheric asymmetry in autism spectrum disorder. *J Vis*; DOI: 10.1167/14.11.3.

Pei F, Baldassi S, Tsai JJ, Gerhard HE & Norcia AM (2017). Development of contrast normalization mechanisms during childhood and adolescence. *Vision Res* **133,** 12–20.

Peirce JW (2007). The potential importance of saturating and supersaturating contrast response functions in visual cortex. *J Vis* **7,** 13.

Petrov Y, Carandini M & McKee S (2005). Two distinct mechanisms of suppression in human vision. *J Neurosci* **25,** 8704–8707.

Polat U & Sagi D (1993). Lateral interactions between spatial channels: Suppression and facilitation revealed by lateral masking experiments. *Vision Res* **33,** 993–999.

Porciatti V, Bonanni P, Fiorentini A & Guerrini R (2000). Lack of cortical contrast gain control in human photosensitive epilepsy. *Nature Neuroscience* **3,** 259–263.

Regan D (1966). Some characteristics of average steady-state and transient responses evoked by modulated light. *Electroencephalogr Clin Neurophysiol* **20,** 238–248.

Regan MP & Regan D (1988). A frequency domain technique for characterizing nonlinearities in biological systems. *Journal of Theoretical Biology* **133,** 293–317.

Ridder WH 3rd (2004). Methods of visual acuity determination with the spatial frequency

sweep visual evoked potential. *Doc Ophthalmol* **109,** 239–247.
Ross J, Speed HD & Morgan MJ (1993). The effects of adaptation and masking on incremental thresholds for contrast. *Vision Res* **33,** 2051–2056.
Shapley RM & Victor JD (1980). The effect of contrast on the non-linear response of the y cell. *J Physiol* **302,** 535–547.
Shibata K, Yamane K, Otuka K & Iwata M (2008). Abnormal visual processing in migraine with aura: A study of steady-state visual evoked potentials. *J Neurol Sci* **271,** 119–126.
Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P & Pollick FE (2009). Vision in autism spectrum disorders. *Vision Res* **49,** 2705–2739.
Skoczenski AM & Norcia AM (1998). Neural noise limitations on infant visual sensitivity. *Nature* **391,** 697–700.
Tadin D, Lappin JS, Gilroy LA & Blake R (2003). Perceptual consequences of centre-surround antagonism in visual motion processing. *Nature* **424,** 312–315.
Tolhurst DJ, Movshon JA & Thompson ID (1981). The dependence of response amplitude and variance of cat visual cortical neurones on stimulus contrast. *Exp Brain Res* **41,** 414–419.
Tsai JJ, Norcia AM, Ales JM & Wade AR (2011). Contrast gain control abnormalities in idiopathic generalized epilepsy. *Annals of Neurology* **70,** 574–582.
Tsai JJ, Wade AR & Norcia AM (2012). Dynamics of normalization underlying masking in human visual cortex. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* **32,** 2783–2789.
Tyler CW & Apkarian PA (1985). Effects of contrast, orientation and binocularity in the pattern evoked potential. *Vision Res* **25,** 755–766.
Tyler CW, Apkarian P, Levi DM & Nakayama K (1979). Rapid assessment of visual function: An electronic sweep technique for the pattern visual evoked potential. *Investigative Ophthalmology & Visual Science* **18,** 703–713.
Vergeer M, Mesik J, Baek Y, Wilmerding K & Engel SA (2018). Orientation-selective contrast adaptation measured with SSVEP. *Journal of Vision* **18,** 2.
Verghese P, Kim Y-J & Wade AR (2012). Attention selects informative neural populations in human V1. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience* **32,** 16379–16390.
Vilidaite G, Norcia AM, West RJH, Elliott CJH, Pei F, Wade AR & Baker DH (2018). Autism sensory dysfunction in an evolutionarily conserved system. *Proceedings Biological Sciences* **285,** 20182255.
Zheng X, Xu G, Zhi Y, Wang Y, Han C, Wang B, Zhang S, Zhang K & Liang R (2019). Objective and quantitative assessment of interocular suppression in strabismic amblyopia based on steady-state motion visual evoked potentials. *Vision Res* **164,** 44–52.