REVIEW

A CASE FOR HUMAN SYSTEMS NEUROSCIENCE

J. L. GARDNER

Laboratory for Human Systems Neuroscience, RIKEN Brain Science Institute, 2-1 Hirosawa, Wako, Saitama 351-0198, Japan

Abstract—Can the human brain itself serve as a model for a systems neuroscience approach to understanding the human brain? After all, how the brain is able to create the richness and complexity of human behavior is still largely mysterious. What better choice to study that complexity than to study it in humans? However, measurements of brain activity typically need to be made non-invasively which puts severe constraints on what can be learned about the internal workings of the brain. Our approach has been to use a combination of psychophysics in which we can use human behavioral flexibility to make quantitative measurements of behavior and link those through computational models to measurements of cortical activity through magnetic resonance imaging. In particular, we have tested various computational hypotheses about what neural mechanisms could account for behavioral enhancement with spatial attention (Pestilli et al., 2011). Resting both on quantitative measurements and considerations of what is known through animal models, we concluded that weighting of sensory signals by the magnitude of their response is a neural mechanism for efficient selection of sensory signals and consequent improvements in behavioral performance with attention. While animal models have many technical advantages over studying the brain in humans, we believe that human systems neuroscience should endeavor to validate, replicate and extend basic knowledge learned from animal model systems and thus form a bridge to understanding how the brain creates the complex and rich cognitive capacities of humans.

This article is part of a Special Issue entitled: Contributions From Different Model Organisms to Brain Research. © 2014 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: attention, selection, contrast–response, fMRI, max-pooling.

Contents

INTRODUCTION

A peculiar phenomenon had taken hold of the elevators of the Meyer building when I first arrived as a post-doc at NYU's Center for Neural Science. Students, post-docs and professors all seemed to have a different algorithm for hitting the buttons on the elevator. Some would simply hit the button for their floor and wait. Others, though, would use different cryptic combinations of buttons, stretching their fingers wide to simultaneously press the floor they wanted and the current floor. For some, the order was apparently crucial – hitting first their floor before reaching for the current floor. Others used the exact opposite order. After inquiring around about this curious behavior, I was earnestly informed that these combinations of button presses were required to make the doors of the elevator close more quickly – a matter of great importance to impatient occupants of the building. But, what could explain the diversity of different techniques I had witnessed? After some time in the department, I developed my own (incompletely tested) theory – that the elevator had a time-out of a few seconds, after which *any* button press, or combination thereof, would trigger the doors to close. Thus, the occupants of the building had all learned various completely different behaviors, all of which produced the same reward of a swift start to the elevator ride.

ADVANTAGES OF HUMAN BEHAVIOR FOR SYSTEMS NEUROSCIENCE

The natural experiment in the Meyer building elevators is not unlike what animals trained to perform systems neuroscience tasks must be encountering; unable to give explicit verbal instructions, experimenters must rely on animals learning tasks implicitly through rewards. But, if humans faced with these situations apparently can learn a variety of different cognitive strategies, can we be sure that implicitly trained animals are learning what we think we are teaching them? Two typically worrisome aspects of implicit animal training are incremental performance improvements and lack of generalization. Often it takes a long period of time to train an animal to do a task as

simple as following a spot of light with their eyes – despite the fact that you could explicitly instruct another person to do this in a single sentence. Performance improves incrementally over the course of weeks, rather that all at once. After long training on one task, a small seemingly trivial change, like modifying the location or color of targets can often require weeks more incremental training. That is, animals can, frustratingly, often fail to generalize. Again, simple explicit instructions given to a human can easily circumvent such problems of generalization. Of course, both humans (as in the Meyer elevators) and animals (Busse et al., 2011) can exhibit superstitious behaviors that do not directly relate to the demands of the task. But, being able to give explicit instructions and the ability to examine the incredibly flexible behavior of humans are considerable advantages for human systems neuroscience.

Underlying what might be considered nuisances of implicitly instructing animals to perform tasks are deep questions about whether animals performing model tasks are good experimental models of the cognitive behaviors they are meant to emulate. To be sure, the difficulties sketched out above are routinely overcome with careful and determined behavioral training and a fantastic wealth of knowledge has been gained from awake behaving physiology experiments with various animal model systems. Nonetheless, both of these troublesome properties of training may influence experimental outcomes. Long training in a single task may affect the very neural systems that one seeks to understand. For example, extended training on a motion discrimination task (Newsome et al., 1989; Britten et al., 1992; Parker and Newsome, 1998) has been associated with neurons in the intermediate and deep layers of the superior colliculus showing motion selectivity to passively viewed stimuli (Horwitz and Newsome, 1999, 2001), a property which they do not exhibit without such extended training (Horwitz et al., 2004). Neural responses may also be different depending on how well animals have been trained to make correct task generalizations. For example, monkeys trained to select the oddball target from a stimulus array display significantly different response properties in the frontal cortex dependent on whether they were trained to always detect a single color target (in which case they do not generalize the task) compared to when they were trained on trials with differently colored oddball targets and exhibit correct generalization of the task (Schall and Hanes, 1993; Bichot et al., 1996). Clearly, both of these examples above represent careful sets of experiments with thoughtful analyses of resulting behavior and physiology which have resulted in an important and deeper understanding of how task training and learning can affect representations in the brain. However, they also point to the possibility that extended, narrow task training without a very careful and thoughtful approach may prejudice behavior to be inflexible, thus extinguishing the very aspect of cognition that is of paramount interest.

Humans as subjects offer distinct advantages for behavioral training, one that we capitalized on with experiments aimed at understanding neural mechanisms that improve behavioral performance with visual spatial attention (Pestilli et al., 2011). Spatial attention was described and its effects rigorously demonstrated through behavioral techniques in humans dating back over a century (Helmholtz, 1867). Endogenous spatial attention can be operationally defined as improved behavioral performance given prior information about the task-relevance of a particular location. It is distinguished from exogenous attention which is captured by abrupt onset of stimuli (Yantis and Jonides, 1984) independent of subject's prior knowledge of target location (Nakayama and Mackeben, 1989). The "improved behavioral performance" part of this definition of endogenous spatial attention is key. How much better is behavioral performance with spatial attention? If behavioral improvements can be quantitatively measured, that sets the benchmark for neural measurements; the quantitative change in behavioral performance without any overt manifestation like physically orienting to a stimulus needs to be explained by changes in neural activity.

Quantitating this improvement in performance is fundamental – if one finds any physiological correlate of attention, how else will one know if that effect is big, small or just enough to explain the behavioral phenomenon? Monkey experiments are the most behaviorally advanced for studying attention in animal models (Moran and Desimone, 1985; Spitzer et al., 1988; Motter, 1993; Treue and Maunsell, 1996; Luck et al., 1997; Treue and Martínez Trujillo, 1999; McAdams and Maunsell, 2000; Reynolds et al., 2000; Cohen and Maunsell, 2009). Numerous neural consequences of spatial attention in elegant behavioral designs have been discovered in monkeys (Desimone and Duncan, 1995; Reynolds and Chelazzi, 2004). However, only a much smaller minority of experiments has tried to account in a quantitative way for how neural changes can account for performance benefits with attention (e.g. Cook and Maunsell, 2002; Cohen and Maunsell, 2009, 2010). Instead, monkeys are often trained to discriminate some change on one target while ignoring similar changes on another target. While this certainly engages selective responding to one set of stimuli, it does not give a quantitative measure of how much behavioral performance is improved with attention.

We started our analysis in Pestilli et al. (2011) with a behavioral paradigm designed to quantitatively measure spatial attention's effect on behavioral performance. Subjects were either cued to one or all stimuli and asked to discriminate a small change in contrast on one of the stimuli, thus encouraging subjects to focus or distribute spatial attention, respectively. By using staircase procedures (Levitt, 1971; Watson and Pelli, 1983) we could measure precisely how much behavioral performance enhancement there was with attention by noting a change in contrast discrimination threshold between focused and distributed attention. Our quantitative behavioral measurements of attention were built on a solid foundation of experimental work in humans that have shown quantifiable effects of attention (Posner, 1980; Pashler, 1998) and set the stage for our examination for what neural mechanisms could have accounted for that change.

MEASURING CORTICAL ACTIVITY IN HUMANS

While using human subjects greatly facilitated gathering quantitative behavioral evidence of spatial attention, what good would such measurements be for understanding brain mechanisms when existing tools to study neural activity in humans are so crude? We measured blood oxygenation level-dependent contrast (BOLD Ogawa et al., 1990, 1992) using magnetic resonance imaging, but the limitations of this technique are well known and have been extensively reviewed and debated (Logothetis, 2008). Fundamentally, BOLD is a poor measure of neural activity because it is not a measure of neural activity, nor is it even really a measure. BOLD is sensitive to the concentration of deoxygenated hemoglobin (Ogawa et al., 1993), but is typically not calibrated to measure this, or any other quantity (Davis et al., 1998; Blockley et al., 2012; Mezer et al., 2013), quantitatively. The concentration of deoxygenated hemoglobin in turn is related to at least three different physiological variables; the cerebral metabolic rate of oxygen consumption, cerebral blood flow and cerebral blood volume (Buxton, 2012), which are all related to neural activity through mechanisms that are just beginning to be understood (Attwell et al., 2010; Bélanger et al., 2011). Given the apparent crudeness of the BOLD measurement, should it not be relegated to asking crude localization questions, rather than the types of mechanistic questions about how to quantitatively link neural responses in humans to behavioral enhancement with attention that we were interested in?

In fact, BOLD measurements, when deployed with finesse, for example in defining visual field representations, are currently the most refined tool that we have. Over a century ago, another technology, the high-powered rifle, left narrow destructive paths of bullets through the cortex of Japanese soldiers and left an awful legacy of the Russo Japanese war. But from careful study of the visual field deficits in these injured soldiers, Tatsuji Inouye determined the topography of primary visual cortex and correctly deduced that the representation was flipped upside down, the fovea was at the occipital pole, and that there was a cortical magnification of the foveal representation (Inouye, 2000; Adams and Horton, 2001). Modern imaging techniques developed just after the introduction of BOLD (Engel et al., 1994; Sereno et al., 1995; DeYoe et al., 1996), make measurements of visual fields routine in normal human subjects – a methodological triumph over analyses based on lesion patients. The technique has rapidly led to the characterization of multiple topographic representations in the visual cortex, some of which may even be unique to humans (Schluppeck et al., 2005; Larsson and Heeger, 2006; Pitzalis et al., 2006; Sereno and Huang, 2006; Swisher et al., 2007; Wandell et al., 2007; Silver and Kastner, 2009; Wandell and Winawer, 2011). In monkeys (Brewer et al., 2002) it can establish in one experiment the numerous topographic representations of the visual world that took decades of research to find with single-unit measurements (Zeki, 1978; Van Essen et al., 1992) and provide quick resolution to long-debated representations (Kaas and Lyon, 2001) – though it should

be noted that contamination by imaging artifacts from sinuses (Winawer et al., 2010) may lead to considerable debate in visual field maps made from functional imaging data (Tootell and Hadjikhani, 2001; Brewer et al., 2005; Hansen et al., 2007). Even in the rodent system which is widely considered to have among the best tools available for systems neuroscience, topographic mapping techniques borrowed from human imaging (Kalatsky and Stryker, 2003) coupled with optical measurements of intrinsic signals akin to BOLD (Grinvald et al., 1986) are used to map visual field representations (Schuett et al., 2002; Andermann et al., 2011; Marshel et al., 2011). In our hands, retinotopic mapping in humans with BOLD imaging allowed us to study the coordinate frame (Gardner et al., 2008) and modulations by eye position (Merriam et al., 2013) across multiple visual areas in the brain in single experiments (see also: Sereno and Huang, 2006; d'Avossa et al., 2007; McKyton and Zohary, 2007; Golomb and Kanwisher, 2012). Contrast that to decades of animal experiments in monkey parietal cortex which were required to first establish these same properties (Andersen and Buneo, 2002). Topographic representations allowed us in our attention experiments to compare responses across multiple visual areas, but even more importantly to measure responses separately for different targets based on their spatial localization. Thus, BOLD measurements excel at measuring topographic properties of visual representations which is a particularly useful property for addressing systems neuroscience questions.

Beyond topography, BOLD imaging is a good tool for making measurements of contrast–response in visual cortex – a measurement critical for linking our quantitative behavioral measurements of contrast sensitivity enhancements with spatial attention to underlying neural mechanisms. Image contrast can be measured in a variety of different ways (Bex and Makous, 2002) but corresponds to the overall difference between dark and light portions of an image. Image contrast is a fundamental property of visual stimuli in that it controls visibility, just as when one increases contrasts on a video display, the higher the contrast the more visible the stimulus. Neural responses in visual cortex of mice (Busse et al., 2011), cats and monkeys (Albrecht and Hamilton, 1982; Sclar et al., 1990) all show monotonically increasing responses with contrast (but see Sani et al., 2013), termed a contrast–response function. BOLD measurements in visual cortex of humans behave exactly as expected if they are reflective of a population of neurons with monotonically increasing contrast response (Tootell and Taylor, 1995; Boynton et al., 1996, 1999; Tootell et al., 1998; Logothetis et al., 2001; Avidan et al., 2002; Olman et al., 2004; Gardner et al., 2005). Indeed, only a single scaling factor is needed to match contrast–response between BOLD measurements and those from similarly measured single-units (Heeger et al., 2000). Simultaneous measures of hemodynamic signals with optical imaging techniques in experimental animals and neural response have found a linear (Cardoso et al., 2012) or threshold-linear relationship (Logothetis et al., 2001) between the two. The advantage of being able to

make BOLD measurements simultaneously from multiple topographically defined visual areas has shown that much like several decades of single-unit studies have found (Rolls and Baylis, 1986; Sclar et al., 1990; Cheng et al., 1994), higher-order visual areas are more contrast invariant than lower-order visual areas. That is, as soon as contrast is increased enough to make a stimulus visible, higher-order visual areas respond with near maximal activity (Tootell et al., 1995; Avidan et al., 2002), a property that may be dependent on attention (Murray and He, 2006; Yue et al., 2010).

Contrast–response measurements were of particular interest to us because they have been studied extensively in animal experiments of spatial attention, showing a variety of effects that would be potentially measurable with BOLD. Early measurements of contrast–response with attention in monkeys showed a "contrast-gain" shift with attention – essentially the whole contrast–response function shifted to the left (Reynolds et al., 2000; Martínez-Trujillo and Treue, 2002). This change could be viewed as equivalent to physically turning up the contrast of a stimulus and thus make it more visible with attention. However, other studies argued for multiplicative gain changes in response with attention (Lee and Maunsell, 2010) which have the virtue of not changing the bandwidth of tuning functions (McAdams and Maunsell, 1999). When applied to contrast–response they correspond to changes across all contrasts which would make difference in contrast at all levels of contrast potentially more discriminable. Still other experiments argued for additive shifts of contrast–response dependent on visibility (Thiele et al., 2009; Pooresmaeili et al., 2010). These discrepancies in results from different studies may be the result of changes in the area over which animal subjects attended in various studies (Reynolds and Heeger, 2009), a theory for which now there is some experimental support in humans (Herrmann et al., 2010; Itthipuripat et al., 2014). Subsequent modeling efforts we have made (Hara et al., 2014) suggest that if the theory is correct, some of the variability in measured response patterns across different single units (Williford and Maunsell, 2006) could result in the additive shifts in contrast–response that we and others (Buracas and Boynton, 2007; Li et al., 2008; Murray, 2008; Pestilli et al., 2011) have measured with BOLD. Taken together, these various changes in contrast–response reported from the awake-behaving monkey literature were very suggestive that effects of attention on contrast–response were large and potentially measurable with BOLD in humans, but would BOLD be sensitive enough to pick up these changes?

Our experience with studying changes to contrast–response with adaptation suggested that BOLD measurements would be sensitive enough to pick-up any of these potential changes with attention. A well-known property of contrast–response is that it shifts horizontally with adaptation to center around the adapting contrast (Ohzawa et al., 1982, 1985; Sclar et al., 1985; Bonds, 1991; Kohn and Movshon, 2003; Solomon et al., 2004). That is, a remarkable change to contrast–response occurs after several seconds expo-sure to a stimulus presented with some adaptation contrast – the whole contrast–response shifts to center around the adapting contrast. This shift centers the most sensitive part of the dynamic range of the contrast–response around the adapted contrast, potentially making observers more sensitive to contrast changes that are likely to occur in the environment. Measuring contrast–response changes with adaptation we were able to verify, for the first time, this property in humans (Gardner et al., 2005). In doing so, we also discovered a peculiarity of contrast–response in some higher visual areas like hV4; responses less faithfully represented overall contrast level, but instead increased regardless of whether contrast was increased or decreased and thus appeared to respond to changes in contrast. We later found a similar effect for motion coherence (Costagli et al., 2014) and while our observations were originally made using fMRI in humans, subsequent work in monkeys suggests that there may be non-monotonic tuning curves for contrast in V4 (Sani et al., 2013) which could underlay the effects we originally discovered in humans. In summary, our experiments on contrast adaptation formed the basis for our attention experiments because they bolstered the case that BOLD measurements of contrast–response were picking up activity as expected about the population of neurons responding to contrast. Moreover, measurements of adaptation-related changes in BOLD contrast–response suggested that it would be possible to measure contrast–response changes with a cognitive factor like attention.

LINKING HUMAN CORTICAL ACTIVITY TO BEHAVIOR WITH COMPUTATIONAL MODELS

Having both a quantitative behavioral measure of the benefits of spatial attention and a quantitative measure of cortical response related to that perception we needed a model to connect the two measurements – something that was already well developed in the human psychophysics literature (Nachmias and Sansbury, 1974; Stromeyer and Klein, 1974; Foley and Legge, 1981). In particular, if one knows the relationship between contrast and response, simple models based on signal detection in which psychophysical sensitivity (that is d') can be related to difference in response divided by the standard deviation can be used to predict behavioral effects. These models already had success in the study of contrast sensitivity (Boynton et al., 1999) and with surround suppression (Zenger-Landolt and Heeger, 2003) and we used them to study how attention effects could be modeled. The behavioral effects of attention that we measured quantitatively suggested large changes in the slope of the contrast–response function, but, to our surprise, these was no evidence for such changes in the BOLD measurements we made in Pestilli et al. (2011).

As these simple models of contrast sensitivity could not quantitatively explain our measurements, we turned to another set of quantitative models also largely coming from the human psychophysical literature which focused on the selection of signals. In particular, our BOLD measurements found little evidence for changes in the

slope of contrast–response as would have been predicted by signal detection models, but did, as has been reported by many groups (Buracas and Boynton, 2007; Li et al., 2008; Murray, 2008; Chen and Seidemann, 2012), find large increases in response at cued locations for all contrast–additive offsets. We reasoned that these changes in contrast–response could improve behavior by aiding in the selection of the correct sensory signals for cognitive processing. That is, when attention is focused on a single target, the response to that stimulus is increased in early visual cortex and as a consequence that signal is selected for perceptual processing. When attention is distributed to multiple locations, all the responses to the stimuli have similar magnitude which does not lead to any advantage for any particular signal for pooling and thus responses are averaged together resulting in poor performance because relevant and irrelevant responses are averaged together. Thus, in our model, the larger the neural signal, the more efficiently it would be selected for pooling. The model that we developed to quantitatively link our BOLD measurements to behavioral measurements was built on theoretical models of attention (Pelli, 1985; Lee et al., 1999; Itti and Koch, 2001) and search (Palmer et al., 2000; Eckstein et al., 2009) which have focused on how sensory signals are weighted in perception. We have found that the model can also reproduce behavioral effects of parametrically changing the prior probability that a target is relevant (Hara and Gardner, 2012) and have validated a prediction that the model makes – that simply increasing the contrast of distractors and thereby increasing their response magnitude would disrupt performance (Pestilli et al., 2011). These effects of distractors are similar to other stimulus-driven (Palmer and Moore, 2009; Yigit-Elliott et al., 2011) and transient (Nakayama and Mackeben, 1989) attention effects that have previously been reported to capture attention with abrupt onsets (Yantis and Jonides, 1984).

HUMAN SYSTEMS NEUROSCIENCE AS A LINK IN OUR UNDERSTANDING OF THE BRAIN

We concluded that an efficient selection mechanism could account for the attentional behavioral enhancement we observed, but could the inferences that we made be on more solid ground if we had used animal models in which more invasive, yet potentially revealing, experimental techniques would have been possible? Indeed, many aspects of neural responses that have been associated with attentional enhancement, like reductions in variability and correlation (Cohen and Maunsell, 2009; Mitchell et al., 2009), increased efficacy of synaptic transmission (Briggs et al., 2013) or changes in neural synchrony (Fries et al., 2001; Womelsdorf et al., 2006; Gregoriou et al., 2009; Bosman et al., 2012) are likely not measurable with BOLD. Nuanced aspects of neural population dynamics (Churchland et al., 2012; Mante et al., 2013), particularly when neurons show mixed selectivities (Rigotti et al., 2013) that have been associated with flexibility in behavior cannot be easily assessed. Important questions of causality which are typically studied through

inactivation (Lovejoy and Krauzlis, 2010; Zénon and Krauzlis, 2012) or stimulating neural circuitry (Moore and Fallah, 2001; Moore and Armstrong, 2003) are difficult to study in a similar way in humans as technologies like transcranial magnetic stimulation are only beginning to be deployed in ways where they can act to substitute or enhance neural signals rather than just disrupt them (Abrahamyan et al., 2011). Despite all this, it is important to remember that all modes of study of the brain are limited in one way or another. While it is always tempting to view one's own model as some sort of pinnacle, in reality, each experiment we conduct, no matter what model system we use, only gives us a tiny window into the massively complex and still beautifully mysterious workings of our brains.

What role should human systems neuroscience have in the overall pursuit of understanding the brain? Perhaps the biggest caveat for all animal models is simply that they are not the human brain and for many, understanding the human brain is an ultimate goal. This is not to say that knowledge gained from animal experiments cannot be used to make inferences about how the human brain works. But those inferences need to be connected to and validated with measurements in humans. Different measures of brain activity may occasionally lead to seeming contradictions (Boynton, 2011). Rather than take a myopic view through the lens of one's own model system and techniques, we should view these discrepancies as opportunities to seek a unified view of different measures of brain activity and behavior that will lead to new insights. Developments in the study of human cognition (Tenenbaum et al., 2011) provide the possibility of understanding many complex behaviors of humans such as inductive reasoning (Kemp and Tenenbaum, 2008) or language processing and acquisition (Chater and Manning, 2006; Frank and Goodman, 2012) that are difficult, if not impossible, to study in animal systems. The goal of human systems neuroscience should be to link our developing understanding of human higher cognition with the burgeoning knowledge of the neural circuitry that give rise to these unfathomably rich abilities that our brains are capable of.

CONFLICT OF INTEREST

The authors have no financial or non-financial competing interests with regard to this work.

REFERENCES

Abrahamyan A, Clifford CWG, Arabzadeh E, Harris JA (2011) Improving visual sensitivity with subthreshold transcranial magnetic stimulation. J Neurosci 31:3290–3294.

Adams DL, Horton JC (2001) What you see... visual disturbances following gunshot wounds of the cortical visual area. Nature 412:482–483.

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

Andermann ML, Kerlin AM, Roumis DK, Glickfeld LL, Reid RC (2011) Functional specialization of mouse higher visual cortical areas. Neuron 72:1025–1039.

Andersen RA, Buneo CA (2002) Intentional maps in posterior parietal cortex. Annu Rev Neurosci 25:189–220.

Attwell D, Buchan AM, Charpak S, Lauritzen M, MacVicar BA, Newman EA (2010) Glial and neuronal control of brain blood flow. Nature 468:232–243.

Avidan G, Harel M, Hendler T, Ben-Bashat D, Zohary E, Malach R (2002) Contrast sensitivity in human visual areas and its relationship to object recognition. J Neurophysiol 87:3102–3116.

Bélanger M, Allaman I, Magistretti PJ (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab 14:724–738.

Bex PJ, Makous W (2002) Spatial frequency, phase, and the contrast of natural images. J Opt Soc Am A Opt Image Sci Vis 19:1096–1106.

Bichot NP, Schall JD, Thompson KG (1996) Visual feature selectivity in frontal eye fields induced by experience in mature macaques. Nature 381:697–699.

Blockley NP, Griffeth VEM, Simon AB, Buxton RB (2012) A review of calibrated blood oxygenation level-dependent (BOLD) methods for the measurement of task-induced changes in brain oxygen metabolism. NMR in biomedicine 26:987–1003.

Bonds AB (1991) Temporal dynamics of contrast gain in single cells of the cat striate cortex. Vis Neurosci 6:239–255.

Bosman CA, Schoffelen J-M, Brunet N, Oostenveld R, Bastos AM, Womelsdorf T, Rubehn B, Stieglitz T, De Weerd P, Fries P (2012) Attentional stimulus selection through selective synchronization between monkey visual areas. Neuron 75:875–888.

Boynton GM (2011) Spikes, BOLD, attention, and awareness: a comparison of electrophysiological and fMRI signals in V1. J Vis 11. 12–12.

Boynton GM, Engel SA, Glover GH, Heeger DJ (1996) Linear systems analysis of functional magnetic resonance imaging in human V1. J Neurosci 16:4207–4221.

Boynton GM, Demb JB, Glover GH, Heeger DJ (1999) Neuronal basis of contrast discrimination. Vision Res 39:257–269.

Brewer AA, Press WA, Logothetis NK, Wandell BA (2002) Visual areas in macaque cortex measured using functional magnetic resonance imaging. J Neurosci 22:10416–10426.

Brewer AA, Liu J, Wade AR, Wandell BA (2005) Visual field maps and stimulus selectivity in human ventral occipital cortex. Nat Neurosci 8:1102–1109.

Briggs F, Mangun GR, Usrey WM (2013) Attention enhances synaptic efficacy and the signal-to-noise ratio in neural circuits. Nature 499:476–480.

Britten KH, Shadlen MN, Newsome WT, Movshon JA (1992) The analysis of visual motion: a comparison of neuronal and psychophysical performance. J Neurosci 12:4745–4765.

Buracas GT, Boynton GM (2007) The effect of spatial attention on contrast response functions in human visual cortex. J Neurosci 27:93–97.

Busse L, Ayaz A, Dhruv NT, Katzner S, Saleem AB, Schölvinck ML, Zaharia AD, Carandini M (2011) The detection of visual contrast in the behaving mouse. J Neurosci 31:11351–11361.

Buxton RB (2012) Dynamic models of BOLD contrast. NeuroImage 62:953–961.

Cardoso MMB, Sirotin YB, Lima B, Glushenkova E, Das A (2012) The neuroimaging signal is a linear sum of neurally distinct stimulus- and task-related components. Nat Neurosci 15:1298–1306.

Chater N, Manning CD (2006) Probabilistic models of language processing and acquisition. Trends Cogn Sci (Regul Ed) 10:335–344.

Chen Y, Seidemann E (2012) Attentional modulations related to spatial gating but not to allocation of limited resources in primate V1. Neuron 74:557–566.

Cheng K, Hasegawa T, Saleem KS, Tanaka K (1994) Comparison of neuronal selectivity for stimulus speed, length, and contrast in the prestriate visual cortical areas V4 and MT of the macaque monkey. J Neurophysiol 71:2269–2280.

Churchland MM, Cunningham JP, Kaufman MT, Foster JD, Nuyujukian P, Ryu SI, Shenoy KV (2012) Neural population dynamics during reaching. Nature 487:51–56.

Cohen MR, Maunsell JHR (2009) Attention improves performance primarily by reducing interneuronal correlations. Nat Neurosci 12:1594–1600.

Cohen MR, Maunsell JHR (2010) A neuronal population measure of attention predicts behavioral performance on individual trials. Journal of Neuroscience 30:15241–15253.

Cook EP, Maunsell JHR (2002) Attentional modulation of behavioral performance and neuronal responses in middle temporal and ventral intraparietal areas of macaque monkey. J Neurosci 22:1994–2004.

Costagli M, Ueno K, Sun P, Gardner JL, Wan X, Ricciardi E, Pietrini P, Tanaka K, Cheng K (2014) Functional signalers of changes in visual stimuli: cortical responses to increments and decrements in motion coherence. Cereb Cortex 24:110–118.

Davis TL, Kwong KK, Weisskoff RM, Rosen BR (1998) Calibrated functional MRI: mapping the dynamics of oxidative metabolism. Proc Natl Acad Sci U S A 95:1834–1839.

d'Avossa G, Tosetti M, Crespi S, Biagi L, Burr DC, Morrone MC (2007) Spatiotopic selectivity of BOLD responses to visual motion in human area MT. Nat Neurosci 10:249–255.

Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. Annu Rev Neurosci 18:193–222.

DeYoe EA, Carman GJ, Bandettini P, Glickman S, Wieser J, Cox R, Miller D, Neitz J (1996) Mapping striate and extrastriate visual areas in human cerebral cortex. Proc Natl Acad Sci USA 93:2382–2386.

Eckstein MP, Peterson MF, Pham BT, Droll JA (2009) Statistical decision theory to relate neurons to behavior in the study of covert visual attention. Vision Res 49:1097–1128.

Engel SA, Rumelhart DE, Wandell BA, Lee AT, Glover GH, Chichilnisky EJ, Shadlen MN (1994) FMRI of human visual cortex. Nature 369:525.

Foley JM, Legge GE (1981) Contrast detection and near-threshold discrimination in human vision. Vision Res 21:1041–1053.

Frank MC, Goodman ND (2012) Predicting pragmatic reasoning in language games. Science 336. 998–998.

Fries P, Reynolds JH, Rorie AE, Desimone R (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. Science 291:1560–1563.

Gardner JL, Sun P, Waggoner RA, Ueno K, Tanaka K, Cheng K (2005) Contrast adaptation and representation in human early visual cortex. Neuron 47:607–620.

Gardner JL, Merriam EP, Movshon JA, Heeger DJ (2008) Maps of visual space in human occipital cortex are retinotopic, not spatiotopic. J Neurosci 28:3988–3999.

Golomb JD, Kanwisher N (2012) Higher level visual cortex represents retinotopic, not spatiotopic, object location. Cereb Cortex 22:2794–2810.

Gregoriou GG, Gotts SJ, Zhou H, Desimone R (2009) High-frequency, long-range coupling between prefrontal and visual cortex during attention. Science 324:1207–1210.

Grinvald A, Lieke E, Frostig RD, Gilbert CD, Wiesel TN (1986) Functional architecture of cortex revealed by optical imaging of intrinsic signals. Nature 324:361–364.

Hansen KA, Kay KN, Gallant JL (2007) Topographic organization in and near human visual area V4. J Neurosci 27:11896–11911.

Hara Y, Gardner JL (2012) Encoding of graded changes in validity of spatial priors in human visual cortex. In: Asia Pacific Conference on Vision P2-7.

Hara Y, Pestilli F, Gardner JL (2014) Differing effects of attention in single-units and populations are well predicted by heterogeneous tuning and the normalization model of attention. Front Comput Neurosci 8:12.

Heeger DJ, Huk AC, Geisler WS, Albrecht DG (2000) Spikes versus BOLD: what does neuroimaging tell us about neuronal activity? Nat Neurosci 3:631–632.

Helmholtz HV (1867) Helmholtz's treatise on physiological optics. In: The perceptions of vision, Vol. 3 (Southall JPC, ed). 1924 ed., The Optical Society of America.

Herrmann K, Montaser-Kouhsari L, Carrasco M, Heeger DJ (2010) When size matters: attention affects performance by contrast or response gain. Nat Neurosci 13:1554–1559.

Horwitz GD, Newsome WT (1999) Separate signals for target selection and movement specification in the superior colliculus. Science 284:1158–1161.

Horwitz GD, Newsome WT (2001) Target selection for saccadic eye movements: direction-selective visual responses in the superior colliculus. J Neurophysiol 86:2527–2542.

Horwitz GD, Batista AP, Newsome WT (2004) Direction-selective visual responses in macaque superior colliculus induced by behavioral training. Neurosci Lett 366:315–319.

Inouye T (2000) Visual disturbances following gunshot wounds of the cortical visual area. Oxford University Press.

Itthipuripat S, Garcia JO, Rungratsameetaweemana N, Sprague TC, Serences JT (2014) Changing the spatial scope of attention alters patterns of neural gain in human cortex. J Neurosci 34:112–123.

Itti L, Koch C (2001) Computational modelling of visual attention. Nat Rev Neurosci 2:194–203.

Kaas JH, Lyon DC (2001) Visual cortex organization in primates: theories of V3 and adjoining visual areas. Prog Brain Res 134:285–295.

Kalatsky VA, Stryker MP (2003) New paradigm for optical imaging: temporally encoded maps of intrinsic signal. Neuron 38:529–545.

Kemp C, Tenenbaum JB (2008) The discovery of structural form. Proc Natl Acad Sci U S A 105:10687–10692.

Kohn A, Movshon JA (2003) Neuronal adaptation to visual motion in area MT of the macaque. Neuron 39:681–691.

Larsson J, Heeger DJ (2006) Two retinotopic visual areas in human lateral occipital cortex. J Neurosci 26:13128–13142.

Lee J, Maunsell JHR (2010) The effect of attention on neuronal responses to high and low contrast stimuli. J Neurophysiol 104:960–971.

Lee DK, Itti L, Koch C, Braun J (1999) Attention activates winner-take-all competition among visual filters. Nat Neurosci 2:375–381.

Levitt H (1971) Transformed up-down methods in psychoacoustics. J Acoust Soc Am 49(Suppl. 2):467.

Li X, Lu Z-L, Tjan BS, Dosher BA, Chu W (2008) Blood oxygenation level-dependent contrast response functions identify mechanisms of covert attention in early visual areas. Proc Natl Acad Sci U S A 105:6202–6207.

Logothetis NK (2008) What we can do and what we cannot do with fMRI. Nature 453:869–878.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A (2001) Neurophysiological investigation of the basis of the fMRI signal. Nature 412:150–157.

Lovejoy LP, Krauzlis RJ (2010) Inactivation of primate superior colliculus impairs covert selection of signals for perceptual judgments. Nat Neurosci 13:261–266.

Luck SJ, Chelazzi L, Hillyard SA, Desimone R (1997) Neural mechanisms of spatial selective attention in areas V1, V2, and V4 of macaque visual cortex. J Neurophysiol 77:24–42.

Mante V, Sussillo D, Shenoy KV, Newsome WT (2013) Context-dependent computation by recurrent dynamics in prefrontal cortex. Nature 503:78–84.

Marshel JH, Garrett ME, Nauhaus I, Callaway EM (2011) Functional specialization of seven mouse visual cortical areas. Neuron 72:1040–1054.

Martínez-Trujillo J, Treue S (2002) Attentional modulation strength in cortical area MT depends on stimulus contrast. Neuron 35:365–370.

McAdams CJ, Maunsell JH (1999) Effects of attention on orientation-tuning functions of single neurons in macaque cortical area V4. J Neurosci 19:431–441.

McAdams CJ, Maunsell JH (2000) Attention to both space and feature modulates neuronal responses in macaque area V4. J Neurophysiol 83:1751–1755.

McKyton A, Zohary E (2007) Beyond retinotopic mapping: the spatial representation of objects in the human lateral occipital complex. Cereb Cortex 17:1164–1172.

Merriam EP, Gardner JL, Movshon JA, Heeger DJ (2013) Modulation of visual responses by gaze direction in human visual cortex. J Neurosci 33:9879–9889.

Mezer A, Yeatman JD, Stikov N, Kay KN, Cho N-J, Dougherty RF, Perry ML, Parvizi J, Hua LH, Butts-Pauly K, Wandell BA (2013) Quantifying the local tissue volume and composition in individual brains with magnetic resonance imaging. Nat Med 19:1667–1672.

Mitchell JF, Sundberg KA, Reynolds JH (2009) Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4. Neuron 63:879–888.

Moore T, Armstrong KM (2003) Selective gating of visual signals by microstimulation of frontal cortex. Nature 421:370–373.

Moore T, Fallah M (2001) Control of eye movements and spatial attention. Proc Natl Acad Sci USA 98:1273–1276.

Moran J, Desimone R (1985) Selective attention gates visual processing in the extrastriate cortex. Science 229:782–784.

Motter BC (1993) Focal attention produces spatially selective processing in visual cortical areas V1, V2, and V4 in the presence of competing stimuli. J Neurophysiol 70:909–919.

Murray SO (2008) The effects of spatial attention in early human visual cortex are stimulus independent. J Vis 8:2.1–2.11.

Murray SO, He S (2006) Contrast invariance in the human lateral occipital complex depends on attention. Curr Biol 16:606–611.

Nachmias J, Sansbury RV (1974) Letter: grating contrast: discrimination may be better than detection. Vision Res 14:1039–1042.

Nakayama K, Mackeben M (1989) Sustained and transient components of focal visual attention. Vision Res 29:1631–1647.

Newsome WT, Britten KH, Movshon JA (1989) Neuronal correlates of a perceptual decision. Nature 341:52–54.

Ogawa S, Lee TM, Kay AR, Tank DW (1990) Brain magnetic resonance imaging with contrast dependent on blood oxygenation. Proc Natl Acad Sci U S A 87:9868–9872.

Ogawa S, Tank DW, Menon R, Ellermann JM, Kim SG, Merkle H, Ugurbil K (1992) Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc Natl Acad Sci U S A 89:5951–5955.

Ogawa S, Menon RS, Tank DW, Kim SG, Merkle H, Ellermann JM, Ugurbil K (1993) Functional brain mapping by blood oxygenation level-dependent contrast magnetic resonance imaging. A comparison of signal characteristics with a biophysical model. Biophys J 64:803–812.

Ohzawa I, Sclar G, Freeman RD (1982) Contrast gain control in the cat visual cortex. Nature 298:266–268.

Ohzawa I, Sclar G, Freeman RD (1985) Contrast gain control in the cat's visual system. J Neurophysiol 54:651–667.

Olman CA, Ugurbil K, Schrater P, Kersten D (2004) BOLD fMRI and psychophysical measurements of contrast response to broadband images. Vision Res 44:669–683.

Palmer J, Moore CM (2009) Using a filtering task to measure the spatial extent of selective attention. Vision Res 49:1045–1064.

Palmer J, Verghese P, Pavel M (2000) The psychophysics of visual search. Vision Res 40:1227–1268.

Parker AJ, Newsome WT (1998) Sense and the single neuron: probing the physiology of perception. Annu Rev Neurosci 21:227–277.

Pashler HE (1998) The psychology of attention. Cambridge, MA: MIT Press.

Pelli DG (1985) Uncertainty explains many aspects of visual contrast detection and discrimination. J Opt Soc Am A 2:1508–1532.

Pestilli F, Carrasco M, Heeger DJ, Gardner JL (2011) Attentional enhancement via selection and pooling of early sensory responses in human visual cortex. Neuron 72:832–846.

Pitzalis S, Galletti C, Huang R-S, Patria F, Committeri G, Galati G, Fattori P, Sereno MI (2006) Wide-field retinotopy defines human cortical visual area v6. J Neurosci 26:7962–7973.

Pooresmaeili A, Poort J, Thiele A, Roelfsema PR (2010) Separable codes for attention and luminance contrast in the primary visual cortex. J Neurosci 30:12701–12711.

Posner MI (1980) Orienting of attention. Q J Exp Psychol 32:3–25.

Reynolds JH, Chelazzi L (2004) Attentional modulation of visual processing. Annu Rev Neurosci 27:611–647.

Reynolds JH, Heeger DJ (2009) The normalization model of attention. Neuron 61:168–185.

Reynolds JH, Pasternak T, Desimone R (2000) Attention increases sensitivity of V4 neurons. Neuron 26:703–714.

Rigotti M, Barak O, Warden MR, Wang X-J, Daw ND, Miller EK, Fusi S (2013) The importance of mixed selectivity in complex cognitive tasks. Nature 497:585–590.

Rolls ET, Baylis GC (1986) Size and contrast have only small effects on the responses to faces of neurons in the cortex of the superior temporal sulcus of the monkey. Exp Brain Res 65:38–48.

Sani I, Santandrea E, Golzar A, Morrone MC, Chelazzi L (2013) Selective tuning for contrast in macaque area v4. J Neurosci 33:18583–18596.

Schall JD, Hanes DP (1993) Neural basis of saccade target selection in frontal eye field during visual search. Nature 366:467–469.

Schluppeck D, Glimcher P, Heeger DJ (2005) Topographic organization for delayed saccades in human posterior parietal cortex. J Neurophysiol 94:1372–1384.

Schuett S, Bonhoeffer T, Hübener M (2002) Mapping retinotopic structure in mouse visual cortex with optical imaging. J Neurosci 22:6549–6559.

Sclar G, Ohzawa I, Freeman RD (1985) Contrast gain control in the kitten's visual system. J Neurophysiol 54:668–675.

Sclar G, Maunsell JH, Lennie P (1990) Coding of image contrast in central visual pathways of the macaque monkey. Vision Res 30:1–10.

Sereno MI, Huang R-S (2006) A human parietal face area contains aligned head-centered visual and tactile maps. Nat Neurosci 9:1337–1343.

Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RB (1995) Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. Science 268:889–893.

Silver MA, Kastner S (2009) Topographic maps in human frontal and parietal cortex. Trends Cogn Sci (Regul Ed) 13:488–495.

Solomon SG, Peirce JW, Dhruv NT, Lennie P (2004) Profound contrast adaptation early in the visual pathway. Neuron 42:155–162.

Spitzer H, Desimone R, Moran J (1988) Increased attention enhances both behavioral and neuronal performance. Science 240:338–340.

Stromeyer CF, Klein S (1974) Spatial frequency channels in human vision as asymmetric (edge) mechanisms. Vision Res 14:1409–1420.

Swisher JD, Halko MA, Merabet LB, McMains SA, Somers DC (2007) Visual topography of human intraparietal sulcus. J Neurosci 27:5326–5337.

Tenenbaum JB, Kemp C, Griffiths TL, Goodman ND (2011) How to grow a mind: statistics, structure, and abstraction. Science 331:1279–1285.

Thiele A, Pooresmaeili A, Delicato LS, Herrero JL, Roelfsema PR (2009) Additive effects of attention and stimulus contrast in primary visual cortex. Cereb Cortex 19:2970–2981.

Tootell RB, Hadjikhani N (2001) Where is "dorsal V4" in human visual cortex? Retinotopic, topographic and functional evidence. Cereb Cortex 11:298–311.

Tootell RB, Taylor JB (1995) Anatomical evidence for MT and additional cortical visual areas in humans. Cereb Cortex 5:39–55.

Tootell RB, Reppas JB, Kwong KK, Malach R, Born RT, Brady TJ, Rosen BR, Belliveau JW (1995) Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. J Neurosci 15:3215–3230.

Tootell RB, Hadjikhani NK, Vanduffel W, Liu AK, Mendola JD, Sereno MI, Dale AM (1998) Functional analysis of primary visual cortex (V1) in humans. Proc Natl Acad Sci U S A 95:811–817.

Treue S, Martínez Trujillo JC (1999) Feature-based attention influences motion processing gain in macaque visual cortex. Nature 399:575–579.

Treue S, Maunsell JH (1996) Attentional modulation of visual motion processing in cortical areas MT and MST. Nature 382:539–541.

Van Essen DC, Anderson CH, Felleman DJ (1992) Information processing in the primate visual system: an integrated systems perspective. Science 255:419–423.

Wandell BA, Winawer J (2011) Imaging retinotopic maps in the human brain. Vision Res 51:718–737.

Wandell BA, Dumoulin SO, Brewer AA (2007) Visual field maps in human cortex. Neuron 56:366–383.

Watson AB, Pelli DG (1983) QUEST: a Bayesian adaptive psychometric method. Percept Psychophys 33:113–120.

Williford T, Maunsell JHR (2006) Effects of spatial attention on contrast response functions in macaque area V4. J Neurophysiol 96:40–54.

Winawer J, Horiguchi H, Sayres RA, Amano K, Wandell BA (2010) Mapping hV4 and ventral occipital cortex: the venous eclipse. J Vis 10:1.

Womelsdorf T, Fries P, Mitra PP, Desimone R (2006) Gamma-band synchronization in visual cortex predicts speed of change detection. Nature 439:733–736.

Yantis S, Jonides J (1984) Abrupt visual onsets and selective attention: evidence from visual search. J Exp Psychol Hum Percept Perform 10:601–621.

Yigit-Elliott S, Palmer J, Moore CM (2011) Distinguishing blocking from attenuation in visual selective attention. Psychol Sci 22:771–780.

Yue X, Cassidy BS, Devaney KJ, Holt DJ, Tootell RBH (2010) Lower-level stimulus features strongly influence responses in the fusiform face area. Cereb Cortex 21:35–47.

Zeki SM (1978) Functional specialisation in the visual cortex of the rhesus monkey. Nature 274:423–428.

Zenger-Landolt B, Heeger DJ (2003) Response suppression in V1 agrees with psychophysics of surround masking. J Neurosci 23:6884–6893.

Zénon A, Krauzlis RJ (2012) Attention deficits without cortical neuronal deficits. Nature 489:434–437.