Inverse effectiveness and BOLD fMRI

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Blood oxygenation-level dependent (BOLD) fMRI is an example of a non-invasive technique for measuring human brain activation. Before the advent of techniques like fMRI, the study of neural mechanisms was often carried out in non-human animals using single-unit recording. These neurophysiological studies established many principles for understanding multisensory processing at the level of single neurons (Meredith et al. 1983), and continue to improve our understanding of multisensory mechanisms at that level (Stein et al. 2008). Unlike single-unit recordings, BOLD fMRI measurements reflect the combined activation of *populations* of thousands of neurons. Thus, an interesting problem in cognitive neuroscience research is relating BOLD fMRI measurements to the underlying single-unit responses. In the field of multisensory processes, an interesting (and controversial) problem is determining whether or not a population of neurons contains sub-populations of neurons that would be considered multisensory if measured at the single-unit level. Over the last decade, several criteria have been suggested for inferring multisensory integration. Here, we will briefly review the criteria used with single-unit recording, then review the controversy surrounding the criteria used with BOLD fMRI, and finally suggest a new criterion for BOLD fMRI, based on the principle of inverse effectiveness.

Multisensory enhancement in single neurons

Populations of neurons measured using fMRI contain mixtures of unisensory and multisensory neurons. Unisensory neurons produce significant neural activity (measured as an increase in spike count above spontaneous baseline) with only one modality of sensory input, and this response is not modulated by concurrent input from any other sensory modality. Bi-modal neurons produce significant neural activity with two (or more) modalities of unisensory input (Meredith et al. 1983; Stein et al. 2008). Most bi-modal neurons are also considered multisensory, although this can only be tested using multisensory stimuli. When a multisensory stimulus is presented under conditions of spatial and temporal congruence, many bi-modal neurons produce activity that is greater than the maximum activity produced with either unisensory stimulus. This principle of multisensory enhancement is also called the maximum criterion or rule and can be shown symbolically as $S_{12} > S_1 \vee S_2$, where S_1 and S_2 are the responses with unisensory stimuli from two different sensory modalities, S_{12} is the response with a multisensory stimulus, and $\vee$ is the maximum operator. In practice, multisensory responses do not always show enhancement (for review, see Stein et al. 2009), but for simplicity and clarity, we will focus on only multisensory enhancement in our explanation below of multisensory BOLD criteria.

Another class of multisensory neurons that was recently discovered are called sub-threshold. They have patterns of activity that look unisensory when they are tested with only unisensory stimuli, for instance, a strong response with S_1, but no response with S_2. Unlike true unisensory neurons, however, when sub-threshold neurons are tested with multisensory stimuli, they show multisensory enhancement (Allman et al. 2008; Allman et al. 2007; Meredith et al. 2009). Sub-threshold neurons will not be explicitly considered below when developing the rationale behind multisensory BOLD criteria, again for simplicity and clarity. Bi-modal (and sub-threshold) neurons that show multisensory enhancement can be subdivided into those that are superadditive and those that are subadditive (Stein et al. 1993; Stein et al. 2009). Superadditive neurons show multisensory activity that exceeds a "superadditivity" criterion that is the *sum* of the unisensory activities (i.e., $S_{12} > S_1 + S_2$). To be clear, though, superadditivity in single-unit studies is not usually used as a criterion for identifying multisensory integration (although see Populin et al. 2002), but instead is used to classify the *degree* of multisensory enhancement.

Multisensory enhancement in BOLD fMRI

There have been two approaches to developing criteria for assessing multisensory enhancement using BOLD fMRI, one theoretical and one empirical. The theoretical approach is usually to develop appropriate criteria from a model of the underlying population activity based on knowledge of the relation between BOLD activation and single-unit responses. The empirical approach is to use the criteria that accurately identify previously known regions of multisensory integration as such and that do so consistently across different experiments. Theoretical approaches agree that an additive criterion ($S_{12} > S_1+S_2$) captures the hypothetical underlying population activity with multisensory stimuli best (Beauchamp 2005; Calvert et al. 2000; Laurienti et al. 2005; Stevenson et al. 2009a; Stevenson et al. 2009b). Empirical approaches agree, however, that a maximum criterion (i.e., $S_{12} > S_1 \vee S_2$) produces the most consistent results in known multisensory brain regions (Beauchamp 2005; Beauchamp et al. 2004; Doehrmann et al. 2008; Hein et al. 2007; van Atteveldt et al. 2007).

The first theory-driven attempt to create a principle for studying multisensory phenomena specific to population-based BOLD fMRI measures was superadditivity (Calvert et al. 2000), which we will refer to as "exceeding the additive criterion" to differentiate it from superadditivity in single units. In her original fMRI study Calvert used audio and visual presentations of speech (talking heads) and isolated an area of the superior temporal sulcus (STS) that produced BOLD activation with a multisensory speech stimulus that was greater than the sum of the BOLD activations with the two unisensory stimuli ($S_{12} > S_1+S_2$). The use of this additive criterion was based on two supportable premises. First, BOLD activation can be modeled as a time-invariant linear system, that is, activation produced by two stimuli presented together can be modeled by summing the activity produced by those same two stimuli presented alone (Boynton et al. 1996; Dale et al. 1997; Glover 1999; Heeger et al. 2002). Second, the null hypothesis to be rejected is that the neuronal population does *not* contain multisensory neurons (Calvert et al. 2000; Calvert et al. 2001; Meredith et al. 1983). Using the additive criterion, the presence of multisensory neurons can be inferred (and the null hypothesis rejected) if activation with the multisensory stimulus exceeds the additive criterion.

The justification for an additive criterion as the null hypothesis is illustrated in Figure 1. The rectangles represent a population of neurons that, importantly, *does not contain multisensory neurons*, and thus represents the null hypothesis. Within the population are two pools of unisensory neurons that respond to only one sensory system or the other (i.e., either S_1 or S_2). In the figure, the population is shown under three different input conditions, unisensory input from S_1, unisensory input from S_2, and multisensory input from a combination of S_1 and S_2. BOLD activation is proportional to the local field potential or the cumulative input to all neurons in the population (Ashby et al. 2008; Logothetis et al. 2004). The modeled population in Figure 1 produces more activation with S_2 than with S_1, possibly because there are more neurons in the S_2 pool than the S_1 pool or possibly because the S_2 neurons produce larger local field potentials. The reason is not important for describing the additive criterion. When the population is stimulated by a multisensory S_{12} stimulus, both pools of neurons are active, producing a larger local field potential and consequently greater BOLD activation. In fact, based on the known relations between single-unit activity, local field potentials, and BOLD activation, the height of the S_{12} bar should be the sum of the S_1 and S_2 bars (i.e., $S_{12} = S_1+S_2$). The modeled S_{12} activation is the same as the additive criterion, suggesting that the additive criterion is the appropriate null hypothesis for assessing multisensory enhancement with BOLD fMRI. Although this chapter deals with BOLD fMRI measurements, similar theoretical arguments have been made for EEG and MEG measurements (Besle et al. 2004).

It has been suggested, however, that in practice the additive criterion is overly conservative and results too often in false negative outcomes (Beauchamp 2005; Goebel et al. 2009). Admittedly, there are only a few fMRI studies that have demonstrated multisensory enhancement that exceeded the additive criterion (Calvert et al. 2000; Calvert et al. 2001; Stevenson et al. 2007; Stevenson et al. 2009a; Werner et al. 2009). Because of this, some researchers prefer the maximum criterion (i.e., $S_{12} > S_1 \vee S_2$), which is more liberal than the additive criterion. Studies using the maximum criterion have consistently found multisensory enhancement in brain regions known to be multisensory (Beauchamp 2005; Beauchamp et al. 2004; Doehrmann et al. 2008; Hein et al. 2007; van Atteveldt et al. 2007). The danger with the maximum criterion, however, is the increased likelihood of false positive outcomes. The model in Figure 1 clearly shows that multisensory stimuli should produce BOLD activation that is greater than the maximum criterion, even when that activation is produced by a population of neurons that contains no multisensory neurons, only unisensory neurons.

Empirically, the maximum criterion seems reliable (Beauchamp 2005; Goebel et al. 2009). However, the fact that, theoretically, the maximum criterion is liberal enough to produce considerable false positive outcomes should cause some concern. The maximum criterion may be practical to use for localizing known multisensory brain regions, but may be too liberal to use in more investigatory analyses, particularly if the results of those analyses are in brain regions that are not known to be multisensory based on invasive techniques. In the remainder of the chapter, we will address theoretical extensions of the additive criterion that provide explanations for why it is too conservative. Because the maximum criterion is more liberal than the additive criterion, these extensions provide an explanation for why the maximum criterion has produced more consistent results than the additive criterion. However, researchers are still cautioned against using the maximum criterion in an investigatory capacity. Although the maximum criterion may produce consistent results in brain regions such as superior temporal cortex (STC), it may be that it produces false positives in other brain regions. To alleviate the problems associated with the additive and maximum criteria, we propose a new additive-differences criterion for assessing multisensory convergence using BOLD fMRI.

Problems with the additive criterion: superadditivity

For simplicity, we have defined the criteria for multisensory integration with respect to only enhancement rather than enhancement and depression. At the level of single units, activity patterns of enhanced and depressed neurons can be analyzed separately. Populations of multisensory neurons will certainly contain pools of both enhanced and depressed neurons, but these pools cannot be analyzed separately. The additive criterion described above was written in terms of enhancement only, that is, $S_{12} > S_1+S_2$. But, the criterion should really be written as $S_{12} \neq S_1+S_2$. The interpretation of activation below the additive criterion ($S_{12} < S_1+S_2$) is not as straightforward as enhancement, because there are many more solutions to the inequality involving different relative weightings of pools of neurons with different activity patterns. Because of this "inverse problem," most researchers have only used the additive criterion to examine activation patterns for enhancement above the criterion (Beauchamp 2005; Calvert et al. 2000; Stevenson et al. 2007; Werner et al. 2009).

Although the inverse problem may be more straightforward with enhancement effects relative to depression effects, there are other problems with enhancement effects that complicate their interpretation. Figure 2b shows a schematic of a multisensory population containing three pools of neurons, two unisensory pools (U_1 and U_2) and one multisensory pool (M). The presence of the third multisensory pool of neurons makes this model an alternative hypothesis to the null hypothesis presented in Figure 1. BOLD activation produced by this model under different sensory conditions is shown in Figure 2a. For example, for the unisensory S_1 condition, BOLD activation is represented as the response of unisensory U_1 neurons combined with the response of multisensory M neurons to the S_1 stimulus (M_{S1}). The response pattern of unisensory U_1 and U_2 neurons is relatively simple: U_1 neurons respond with S_1 and S_{12} stimuli, but not with S_2 stimuli, and vise versa for U_2 neurons. The response patterns of M neurons are more complicated and variable. Different possible response profiles for the pool of M neurons are shown in Figure 2c. Multisensory neurons respond to both unisensory S_1 and S_2 stimuli. They also respond to multisensory stimuli (S_{12}), but the size of that response relative to the responses with unisensory stimuli is variable across neurons. The possibilities for the average activity of a pool of M neurons with S_{12} stimuli vary continuously from depression below the minimum unisensory response to enhancement above the maximum unisensory response (Stein et al. 2009). Of these possibilities, some are more likely than others and some are more theoretically relevant. Three possibilities are examined in Figure 2c and the differential effect of those possibilities is reflected in the BOLD activation shown in Figure 2a.

First, if the averaged activity of M neurons with S_{12} stimuli is greater than the sum of the averaged activity with S_1 and S_2 stimuli ($M_{S12} > M_{S1} + M_{S2}$; superadditivity), BOLD activation is predicted to be greater than the additive criterion ($S_{12} > S_1+S_2$). Second, if the pooled activity of M neurons is greater than the maximum of the pooled activity with S_1 or S_2 stimuli ($M_{S12} > M_{S1} \vee M_{S2}$; maximum rule), BOLD activation is predicted to be less than the additive criterion ($S_{12} < S_1+S_2$). The third possibility is derived from a model based on activity counts from unisensory and multisensory neurons recorded in cat superior colliculus neurons (Laurienti et al. 2005). The recordings suggested that a majority of multisensory neurons were not superadditive and that the neurons that were superadditive showed lower impulse counts overall (i.e., with unisensory and multisensory stimuli) than neurons that were not superadditive. The combination of small numbers and low impulse counts lead to a relatively small contribution to the average single-unit activity by superadditive neurons and hence a relatively small effect on BOLD activation measured in multisensory brain regions. The conclusion from the model was that averaged pooled multisensory activity would not be superadditive, but would exceed the maximum rule. This possibility is quantified as the “Laurienti Model” in Figure 2c. Like the maximum rule, it produces BOLD activation that is less than the additive criterion.

What these three possibilities make clear is that for a population to produce BOLD activation greater than the additive criterion, the average underlying activity of multisensory neurons must be superadditive. Because superadditive neurons represent a minority of multisensory neurons and because they have relatively low impulse counts compared to other multisensory neurons, it is unlikely that the average activity of the multisensory pool will be superadditive. This represents a potential problem with the additive criterion applied to BOLD activation and, consistent with other reports (Beauchamp 2005; Laurienti et al. 2005), suggests that the additive criterion is too conservative.

Problems with the additive criterion: common activation

As described earlier, BOLD fMRI measurements represent the activity of populations of neurons with heterogeneous activity patterns. An assumption, however, was that the different pools of neurons were involved with a similar cognitive operation. It is possible that some neurons in the population are involved in different cognitive operations from those that are being studied. BOLD measurements also reflect the cumulative average of neural activity over time. In other words, BOLD measurements reflect “early” activity associated with sensory processing, but also reflect “late” processing associated with higher-level cognitive operations and overt responses. The theoretical models described above assume that BOLD activation in a region reflects a single sensory (or multisensory) process, but it is more likely that BOLD activation represents a cumulative sum of several processes distributed either through space or time or both. For example, in an experiment where subjects make a response on every trial, it is likely that BOLD activation in many regions reflects response-related activity, either because those brain regions are involved in preparing or executing responses or through feedback from such regions. Even though the activity may occur quite “late” in the trial and may not even occur in the neurons that would be selectively analyzed in a single-unit recording experiment, that activity will be reflected in BOLD measurements from that brain region. For many fMRI experiments, it is likely that this “extraneous” activity is equated across experimental conditions and does not influence the statistical outcome. When two conditions are compared directly using a statistical contrast, the common activation cancels out. But, when using the additive criterion, the common activation is represented twice in the criterion and only once in the multisensory measurement (i.e., S_{12} + *common* > S_1 + S_2 + *2 x common*). Figure 3 shows that adding a small amount of common activation to the simulated activation levels produces a more conservative the additive criterion (Besle et al. 2004).

Problems with the additive criterion: baseline

It is established procedure with fMRI data to transform raw BOLD values to percent signal change values by subtracting the mean activation for the baseline condition and dividing by the baseline. Thus, for BOLD measurements, ‘zero’ is not absolute, but is defined as the activation produced by the baseline condition chosen by the experimenter (Binder et al. 1999; Stark et al. 2001). Statistically, this means that BOLD measurements should be considered an interval scale at best (Stevens 1946). The value of the baseline condition has a different effect on the summed unisensory activations than on the single multisensory activation, because BOLD activation levels are measured relative to an arbitrary baseline. The baseline problem is similar to the common activation problem, that is, the value of the baseline is subtracted from the additive criterion twice, but is subtracted from the multisensory activation only once (i.e., S_{12} - *baseline* > S_1 + S_2 - *2 x baseline*). Greater baseline activation generates a more liberal additive criterion, whereas lesser baseline activation generates a more conservative criterion (James et al. in press).

The baseline and common activation problems are essentially the same mathematically, but they are included as separate issues here to emphasize that the general problem can manifest in more than one way and to provide specific examples of each. A particularly problematic occurrence of the baseline problem can be seen with the use of rapid event-related designs. A typical hemodynamic response requires approximately 12 seconds to return to baseline after stimulation. This would normally mean that trials should be separated by at least 12 s, but because hemodynamic responses are additive, linear models can be used to separate the contribution of one trial from subsequent trials (Boynton et al. 1996; Dale et al. 1997; Glover 1999). Thus, rapid event-related designs with trials closely spaced in time are commonplace in fMRI studies. The overlap of successive hemodynamic responses means that the response never returns to "actual" baseline and it is likely that experiments using different distributions of inter-stimulus intervals (ISI) will produce different arbitrary baseline values from which to measure the experimental conditions. In experiments using a simple subtraction analysis, the effect on baseline may not influence the outcome, however, in multisensory experiments the effect on baseline will influence the strictness of the additive criterion in the same way described above for the baseline and common activation problems.

The effect of different ISI distributions on the additive criterion is demonstrated in Figure 4 with timecourses from three simulated event-related experiments. The data were simulated using standard methods (Ashby et al. 2008; Serences 2004). The underlying functions were generated such that unisensory condition S_2 produced stronger activation than S_1, and that the multisensory condition S_{12} produced activation that was greater than the maximum of S_1 and S_2, but below the additive criterion (Laurienti et al. 2005). Figure 4a shows the results of a simulation using a slow event-related design with a fixed 12 s ISI. The observed BOLD activation data in the left graph was calculated in a standard manner by averaging several data points from the timecourses around the time of peak activation. The observed data shown in Figure 4a are very close to the true data, which is shown for comparison in the right graph. The observed data resemble the true data because the extraction of timecourses is not contaminated by overlap of hemodynamic responses from successive trials.

Figures 4b and 4c illustrate similar simulations, but with ISI distributions that cause overlap of hemodynamic responses from successive trials. Figure 4c shows a simulation with ISIs uniformly distributed across 4, 6, and 8 s. This type of distribution, or distributions with even lower mean ISI, is routinely used in contemporary fMRI experiments (Dale 1999; Serences 2004). The observed BOLD activation data in Figure 4c is lower across all of the conditions compared to the true data shown in Figure 4a. The only difference between the three simulations was the choice of ISI distribution; therefore, the difference in overall level of activation must be due to contamination from overlapping responses with the shorter mean ISI distribution. The effect of the reduction in overall level of activation is shown in the baseline effect graph on the right of Figure 4c. Activation in each of the four conditions was reduced by the same amount compared to the true data. Thus, the effect of reduced activation seen with short mean ISI distributions has a similar effect to a change in baseline or common activation. The white “baseline” bars indicate the level of reduction of activation and illustrate how a change in ISI distribution can influence the outcome of the additive criterion.

Figure 4b shows a simulation with ISIs uniformly distributed across 8, 9, and 10 s, which are rather longer than most fMRI experiments would normally use. The mean ISI is longer than for Figure 4c and shorter than for Figure 4a. The simulation shown in Figure 4b produced a result between the other two. Thus, the overlap of successive hemodynamic responses causes a shift in baseline that is proportional to the amount of overlap. This proportional increase in baseline is illustrated in the baseline effect graphs on the right of Figures 4b and 4c. Although the true data showed multisensory activation that was below the additive criterion, with short ISI distributions, the effect switched, such that the multisensory activation was greater than the additive criterion. In summary, the choice of ISI distribution with event-related designs can influence strictness of the inferences made based on the additive criterion. Distributions with shorter mean ISI increase the overlap between successive trials and artificially raise the baseline value. This in turn causes the additive criterion to be more liberal.

The additive-differences criterion

Any of the problems described above, or some combination of those problems, could explain the inconsistent results of studies that use the additive criterion with BOLD fMRI measurements. It was noted at the beginning of the chapter that the maximum rule has been applied successfully to fMRI studies, however, we also showed theoretically that the maximum rule is likely to produce false positives, that is, produce positive results in brain regions that contain no multisensory neurons. What is needed is a new theoretically-motivated criterion that does not have the theoretical problems associated with the additive and maximum criteria, yet is empirically reliable.

Another established principle of multisensory single-unit recording is the law of inverse effectiveness. Effectiveness in this case means how well the stimulus drives the neurons in question. Unisensory neurons usually decrease their response when the quality of the stimulus, or the signal-to-noise ratio, is degraded. Multisensory neurons also decrease their responses with unisensory and multisensory stimuli when those stimuli are degraded, however, the decrease with multisensory stimuli is not as great as would be predicted by the decreases seen with unisensory stimuli. In other words, as stimulus effectiveness decreases, multisensory enhancement (or gain) increases (Meredith et al. 1986; Stein et al. 2008). By definition, inverse effectiveness only occurs in multisensory neurons; therefore, it can be used as a marker of multisensory integration.

The formula for calculating inverse effectiveness can be written in different ways, but for measurements of activity from single-units, it is often expressed as a change in the difference between activity with the multisensory condition and the maximum of the two unisensory conditions, with the expectation that the difference will increase with decreasing effectiveness. In an experiment with two levels of stimulus quality (high (H) or low (L)), the formula would be

$$M_{S_{12}}^{H} - \left\langle M_1^H \vee M_2^H \right\rangle < M_{S_{12}}^{L} - \left\langle M_1^L \vee M_2^L \right\rangle, \qquad [1]$$

where M is average single-unit activity from the pool of multisensory neurons, with subscripts denoting the stimulus sensory modality, the superscript denoting the stimulus quality, and the symbol $\vee$ denoting a maximum operation. Because the formula for inverse effectiveness uses relative differences to calculate a criterion, it alleviates the problems of common activation and baseline, because the common activation is canceled out by the subtraction operation (Stevenson et al. 2009b). Also, a criterion based on inverse effectiveness alleviates the superadditivity problem, because inverse effectiveness is not based on an assumption about whether the pooled multisensory neurons are super- or sub-additive. In sum, because the criterion for inverse effectiveness can be based on *differences* in activity measurements, it may provide a more consistent assessment of multisensory integration than either the additive or maximum criteria.

Development of the null hypothesis for a criterion based on inverse effectiveness is shown in Figure 5. Similar to the additive criterion, the inverse effectiveness or additive-differences criterion for BOLD measurements is based on a different underlying model than the criterion for single-unit measurements. Because BOLD measurements are unable to isolate only the multisensory neurons, the most appropriate null hypothesis is the sum of the unisensory activation, rather than the maximum. The null hypothesis for the additive-differences criterion is developed similarly to the additive criterion in that it is based on a population with two pools of unisensory neurons (Figure 5c) and the criterion is computed by comparing the sum of two unisensory values to a multisensory value (Figure 5a). The rationale for summing the unisensory values is similar to the rationale behind the additive criterion: change across conditions in the average activity of two pools of neurons should be equal to the sum of the change in the average activity of the individual pools (Figure 5b). Thus, inverse effectiveness with BOLD measurements can be expressed formally in the same was as inverse effectiveness for single-unit measurements, with the exception that the model for combining across sensory systems is the sum instead of the maximum. With two levels of stimulus quality, the formula for BOLD inverse effectiveness would be

$$S_{12}^{H} - \left(S_{1}^{H} + S_{2}^{H}\right) < S_{12}^{L} - \left(S_{1}^{L} + S_{2}^{L}\right).$$

Rather than emphasizing the differences between the multisensory condition and the sum model, this expression can re-written to emphasize the differences between high and low effectiveness,

$$S_{12}^{H} - S_{12}^{L} < \left(S_{1}^{H} - S_{1}^{L}\right) + \left(S_{2}^{H} - S_{2}^{L}\right) \qquad [2]$$

Although the two equations are mathematically equivalent, expressing the terms as differences between high and low effectiveness (Equation 2) emphasizes that a significant effect seen with additive-differences is not predicated on a significant effect with the additive criterion. Equation 2 can be further reduced to

$$\Delta S_{12} < \Delta S_{1} + \Delta S_{2}. \qquad [3]$$

The “delta” terms in Equation 3 can be directly related to the delta terms in Figure 5a, which are derived from Figure 5b. Based on Equation 3, if the multisensory difference is less than the additive-differences criterion, one can infer an interaction between sensory channels, most likely in the form of a third pool of bimodal neurons that show multisensory integration and inverse effectiveness. As will be discussed in more detail below, an interaction is also implied when the multisensory difference is *greater than* the additive-differences criterion. That type of interaction, however, would suggest an effect that was different from inverse effectiveness.

The graphs in Figure 6 summarize and expand some of the ideas presented above, but with a simulation that includes a third pool of multisensory neurons and thus provides an example of an alternative hypothesis. Averaged single-unit activity in multisensory neurons (Figure 6a) is shown for unisensory and multisensory high and low quality stimuli. The changes in single-unit activity as a function of stimulus quality were estimated from single-unit recordings in the superior colliculus of the cat (Alvarado et al. 2007). The pool of multisensory neurons produces more multisensory enhancement under conditions of low quality than under conditions of high quality. One way of formalizing the definition of inverse effectiveness is shown in Equation 1, which is expressed using a *difference* between terms. If S_1 is assigned as the modality that produces the maximum activation, the S_2 terms drop out and the difference formula becomes

$$M_{S_{12}}^{H} - M_{S_1}^{H} < M_{S_{12}}^{L} - M_{S_1}^{L}. \qquad [4]$$

The difference values calculated with the left and right sides of Equation 4 are shown in Figure 6a and labeled ΔH and ΔL, respectively. Note that the difference is greater for the low-quality condition (ΔL) than high-quality condition (ΔH), indicating inverse effectiveness. Inverse effectiveness is often also expressed as a change in percent enhancement or a *ratio* of the terms. This ratio formula replaces differences with quotients and can be expressed as

$$\frac{M_{S_{12}}^{H} - M_{S_1}^{H}}{M_{S_1}^{H}} < \frac{M_{S_{12}}^{L} - M_{S_1}^{L}}{M_{S_1}^{L}}. \qquad [5]$$

Each side of Equation 5 is a percent enhancement term and percent enhancement values calculated with this formula are shown in Figure 6b. In the simulation, the percent enhancement is greater for the low-quality condition than the high-quality condition, which is indicative of inverse effectiveness in the single-unit activity measurements. Although inverse effectiveness is often illustrated with a ratio (Equation 5), we use it here only for comparison with the difference metric (Equation 4).

Analogous to Equation 2, Equation 4 can be re-written to emphasize the differences between high- and low-effectiveness conditions, rather than the differences between multisensory activity and the maximum model. In that form, it is expressed as

$$M_{S_{12}}^{H} - M_{S_{12}}^{L} < M_{S_1}^{H} - M_{S_1}^{L}, \qquad [6]$$

and can be further reduced to

$$\Delta M_{S_{12}} < \Delta M_{S_1}. \qquad [7]$$

Values calculated from the “delta” terms in Equation 7 are shown in Figure 6b. Note that the bars in Figure 6b represent the same conditions as Figure 6a, but are organized to illustrate the calculations in Equation 6. The unisensory difference (ΔM_{S1}) in Figure 6b is greater than the multisensory difference (ΔM_{S12}), which indicates inverse effectiveness. The mathematical equivalence of Equations 4 and 6 is also illustrated in Figures 6a and 6b. The difference between ΔH and ΔL is the same as the difference between ΔM_{S12} and ΔM_{S1}. A significant difference-of-differences indicates inverse effectiveness.

The increase in enhancement between the high- and low-quality conditions in Figure 6a is such that the low-quality condition produces a superadditive multisensory response, whereas the high-quality condition produces a subadditive response in the range proposed by the Laurienti model (Laurienti et al. 2005). This difference is reflected in the predicted BOLD signal change shown in Figure 6c. Stacked bar heights in Figure 6c were derived by combining the unisensory values from Figure 5 with the multisensory values from Figure 6a. BOLD activation for the high-quality multisensory (S_{12}) condition is below the additive criterion ($S_1 + S_2$; dotted line), whereas the activation for the low-quality multisensory condition is above the additive criterion. This illustration reinforces the point that the amount of multisensory enhancement in the averaged pool of multisensory neurons has a strong influence on the interpretation of BOLD activation. If averaged multisensory single-unit activity is sub-additive, as Laurienti et al. suggest, then BOLD activation is suppressed relative to the additive criterion, whereas if averaged multisensory single-unit activity is superadditive, then BOLD activation may be enhanced relative to the additive criterion.

The additive-differences criterion can be calculated using Equation 3. Differences in BOLD activation between high- and low-quality conditions are calculated for each stimulus modality (Figure 6d). The additive-differences criterion is the sum of the unisensory differences and is compared to the multisensory difference (Figure 6e). The result in Figure 6e is consistent with inverse effectiveness, because the multisensory difference is less than the additive-differences criterion. The results of the simulation shown in Figure 6, which is based on findings of inverse effectiveness in empirical recordings of single-unit activity, suggest that the additive-differences criterion is theoretically appropriate for assessing inverse effectiveness and multisensory integration using BOLD fMRI.

Empirical tests of the additive-differences criterion

There is some empirical evidence that inverse effectiveness can be assessed using BOLD fMRI (Kim et al. 2009; Stevenson et al. 2009a; Werner et al. 2009). Figure 7 shows two examples. Results from multisensory superior temporal cortex (mSTC) with audio-visual (AV) stimuli are shown on the left (Figure 7a, 7b) and results from the lateral occipital tactile visual area (LOtv) with visuo-haptic (VH) stimuli are shown on the right (Figure 7c, 7d). The details of these experiments are reported elsewhere (Kim et al. 2009; Stevenson et al. 2009a). In brief, for the AV experiment, stimulus effectiveness was manipulated by changing the stimulus quality (visual contrast and auditory RMS). In Figure 7b, for each stimulus modality (A, V, AV), the left bar is the high stimulus quality (high effectiveness) version and the right bar is the low-quality version. For the VH experiment, stimulus effectiveness was manipulated by changing the similarity of the categories in a two-alternative forced-choice categorization task. Higher similarity led to higher difficulty and lower effectiveness. In Figure 7d, for each stimulus modality (V, H, VH), the left bar is the low stimulus similarity (high effectiveness) version and the right bar is the high-similarity version. Thus, for both Figure 7b and 7d, bars for the high-effectiveness conditions are on the left of each pair of bars. As can be seen from comparison with the additive criterion bars, both experiments produced activation below the additive criterion for both the high- and low-effectiveness conditions. The under-additive result could be due many different combinations of the issues described above.

Figure 7a and 7c show the differences between high- and low-effectiveness conditions for each experiment for each stimulus modality. Both experiments show a pattern of inverse effectiveness, that is, changes to the difficulty of the tasks had a greater influence on unisensory activation than on multisensory activation. Thus, the change in multisensory activation was less than predicted based on the unisensory changes ($\Delta AV < \Delta A + \Delta V$ and $\Delta VH < \Delta V + \Delta H$). It is important to note that the additive-differences criterion was met, even though the additive criterion was not.

Limitations of the additive-differences criterion

The simulation in Figure 6 and the empirical data in Figure 7 provide some evidence that the additive-differences criterion can be used to successfully assess multisensory processes using BOLD fMRI. However, does satisfying the additive-differences criterion indicate the presence of multisensory neurons that are inversely effective? In other words, is inverse effectiveness in BOLD activation the same as inverse effectiveness in single-unit activity? An examination of the equations used to define inverse effectiveness in multisensory neurons and the additive-differences criterion with BOLD activation provides some insights. In Figure 6, BOLD activation with multisensory stimuli is represented by the activity of three pools of neurons, two unisensory and one multisensory, whereas BOLD activation with unisensory stimuli is represented by only two pools of neurons, one unisensory and one multisensory. Equation 1 can be expanded to show these relationships by including terms to separately represent unisensory (U) and multisensory (M) neuronal contributions to the BOLD activation produced by each stimulus type.

$$\begin{aligned}&\left[U_1^H + U_2^H + M_{S_{12}}^H\right] - \left[U_1^L + U_2^L + M_{S_{12}}^L\right]\ldots\\ &< \left(\left[U_1^H + M_{S_1}^H\right] - \left[U_1^L + M_{S_1}^L\right]\right) + \left(\left[U_2^H + M_{S_2}^H\right] - \left[U_2^L + M_{S_2}^L\right]\right).\end{aligned}$$

By cancelling out the unisensory contributions, this simplifies to

$$\left[M_{S_{12}}^H\right] - \left[M_{S_{12}}^L\right] < \left(\left[M_{S_1}^H\right] - \left[M_{S_1}^L\right]\right) + \left(\left[M_{S_2}^H\right] - \left[M_{S_2}^L\right]\right),$$

which can be expressed as

$$\Delta M_{S_{12}} < \Delta M_{S_1} + \Delta M_{S_2}. \qquad [8]$$

First, although the unisensory activity must be accounted for when assessing multisensory phenomena using populations measures – for instance, a decision to use the sum model instead of the maximum model -- it is interesting to notice that the additive-differences criterion is, theoretically, measuring differences in only multisensory activity. Second, Equation 8, which is calculated from the additive-differences metric, is different from Equation 7, which represents the criterion for inverse effectiveness. Thus, the additive-differences criterion with BOLD activation is not the same as the criterion for inverse effectiveness used with singe-unit activity measurements, and satisfying the additive-differences criterion with BOLD activation does not necessarily imply the presence of inversely-effective neurons.

The difference between Equations 7 and 8 is the addition to the right side of Equation 8 of the delta term for the sensory modality that produces the weaker response. If the response to that sensory modality is negligible, then Equation 8 becomes equivalent to Equation 7, in which case, satisfying the additive-differences criterion does imply the presence of inversely effective neurons. It is worthwhile mentioning that this case is plausible, given the recent finding of sub-threshold multisensory neurons that produce negligible activity with one of the two sensory modalities to which they are sensitive (Allman et al. 2009).

Because of the direction of the inequality in Equation 8, if the ΔM_{S2} term is significant, that is if the weaker sensory modality produces significant differences activity across levels of stimulus quality, then the additive-differences criterion becomes more liberal than the inverse effectiveness criterion. As a result, the multisensory pool of neurons does not need to actually be inversely effective to satisfy the additive-differences criterion. There are two implications of this statement. First, if the weaker sensory modality contributes significantly to differences in BOLD activation, then the multisensory pool contains bimodal neurons, which by itself implies neuronal convergence. Second, if the multisensory pool of neurons is inversely effective, the additive-differences criterion will be satisfied. The additive-differences criterion is either less conservative than, or equally conservative to, the inverse-effectiveness criterion. If the multisensory pool of neurons is inversely effective, the additive-differences criterion can be used to demonstrate the significant interaction.

To summarize these two implications, satisfying the additive-differences criterion cannot specify the unique characteristics of the multisensory pool of neurons, such as whether or not they are bimodal, show inverse effectiveness, etc. What satisfying the additive-differences criterion does specify, however, is that there is a pool of multisensory neurons that expresses at least one known characteristic of multisensory neurons, such as bimodal responses or inverse effectiveness. Thus, the additive-differences criterion should not be seen as an indicator of neuronal inverse effectiveness, but rather as a more general assessor of multisensory processes.

The simulations above make the assumption that BOLD activation can be described by a time-invariant linear system. Although there is evidence supporting this assumption (Boynton et al. 1996; Dale et al. 1997; Glover 1999; Heeger et al. 2002), studies using serial presentation of visual stimuli suggest that non-linearities in BOLD activation may exist when stimuli are presented close together in time, that is, closer than a few seconds (Boynton et al. 2003; Friston et al. 1999). Simultaneous presentation could be considered serial presentation with the shortest asynchrony possible. In that case, the deviations from linearity with simultaneous presentation may be substantial. If these non-linearities exist, then the additive models described above would need to be modified. A careful examination of unisensory integration and a comparison of unisensory with multisensory integration could provide valuable insights about the linearity assumption of BOLD responses.

Use of the empirical data shown in Figure 7 to satisfy the additive-differences criterion is based on another assumption, which is that the two levels of effectiveness are selected from a continuous set of levels that are monotonic and linearly related to an experimental variable, such as stimulus quality or task difficulty. For instance, for the AV experiment shown in Figure 6, the levels of stimulus quality were quantified by measuring the levels of signal-to-noise ratio necessary to produce different levels of performance as measured by accuracy. Only two levels were shown in Figure 6, but three levels were measured in the experiment to ensure that the relationship between accuracy and effectiveness was linear. Compared to using the additive criterion, this means that using the additive-differences criterion requires a minimum of two times the experimental conditions, and usually a minimum of three times the conditions to ensure linearity across levels.

A nomenclature for additive-differences

Investigating multisensory processing with BOLD fMRI allows for routine examination of activation patterns across the whole brain, something that is not practical with single-unit recordings. Examination of the whole cortex and subcortical structures provides the possibility that patterns of activation not seen in single-unit recordings could be found that do not obey the principles that have been developed to date. A framework for classifying the mechanisms of multisensory integration must entertain the possibility that there exist mechanisms that have yet to be discovered (De Gelder et al. 2003). The new patterns could be due to different proportions of known classes of neurons or the presence of other classes of multisensory neurons that have not yet been found with single-unit recording. Figure 8 is a diagram depicting four possible outcomes using the additive-differences criterion. The top left quadrant represents the effects shown in Figures 6d, 7b, and 7d that are related to inverse effectiveness. Increases in task difficulty (or decreases in stimulus quality) produce reduced BOLD activation across all stimulus conditions, but the effect on multisensory stimuli is proportionally less than the effect on unisensory stimuli. Because the gain from high to low task difficulty is less for multisensory than unisensory stimuli, we call the effect multisensory gain suppression. Because the relation between task difficulty and BOLD activation is directly proportional, that is, making the task difficult reduces the effectiveness, the effect is called *direct* multisensory gain suppression (or just direct suppression). As described above, direct suppression effects have been seen in single-unit recordings (inverse effectiveness) (Meredith et al. 1986), and in BOLD activation (Kim et al. 2009; Stevenson et al. 2009a; Werner et al. 2009).

In the top right quadrant of Figure 8, increases in task difficulty reduced BOLD activation across all stimulus conditions, however, the effect on multisensory stimuli is proportionally *greater* than on unisensory stimuli. Because the gain from high to low difficulty is greater for multisensory than unisensory stimuli, we call the effect multisensory gain enhancement. Because the relation between difficulty and BOLD activation is directly proportional, we call the effect direct multisensory gain enhancement (direct enhancement). Direct enhancement effects have been seen in single-unit recordings of sub-threshold neurons (Allman et al. 2009). For instance, in a visual sub-threshold neuron, as the quality of the auditory stimulus is increased, neural activity also increases, suggesting some form of mutual potentiation. Direct enhancement has also been observed in BOLD activation patterns with visual-haptic object recognition in occipital and parietal cortex when the visual and haptic stimuli are spatially and temporally incongruent (Kim et al. 2010).

It is possible (or even likely), especially outside brain regions involved in sensory processing, that the relation between difficulty and BOLD activation could be the reverse of that seen in sensory brain regions. That is, as difficulty increases, activation increases. For cases like this, because the relation between difficulty and activation is indirectly proportional, the prefix indirect is used. When multisensory activation shows less proportional gain (in this case calculated as the absolute value of the difference between effectiveness conditions) than the unisensory activation, it is called *indirect* suppression (bottom left quadrant). This effect has been found in the anterior cingulate cortex and areas of the frontal cortex that may be involved in processing task difficulty, uncertainty, or conflict (Brown et al. 2005; Gold et al. 2007; Stevenson et al. 2009b). The final category is indirect enhancement (bottom right quadrant), and to our knowledge, examples of this effect have yet to be discovered.

Conclusions

The additive-differences criterion developed in this chapter escapes the problems associated with the additive and maximum criteria. While developing this criterion, it became clear that measurements taken from populations of neurons, such as BOLD fMRI, can be used to infer the presence of multisensory processing in a brain region. Inferences about specific multisensory principles established at the level of single-unit recordings, however, are much less reliable. With the proper experimental design and the proper criteria, BOLD fMRI measurements are a powerful tool for whole-brain, non-invasive investigation of multisensory processing, a tool that becomes even more powerful when combined with other invasive and non-invasive techniques.

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Figure Captions

Figure 1. A null hypothesis for assessing multisensory integration. Rectangles represent a cluster of voxels. Smaller rectangles represent pools of unisensory neurons within the cluster, with pool U_1 responding preferentially with sensory modality S_1, and U_2 responding with S_2, and both pools responding with multisensory stimuli (S_{12}).

Figure 2. The influence of different patterns of multisensory neural activity on the additive criterion. The symbols are described in Figure 1, except for the addition of a multisensory (M) pool of neurons in (B) that responds with stimuli in either sensory modality. The Possible S_{12} label in (C) designates a set of different hypothetical response characteristics of a pool of M neurons when presented with a multisensory stimulus.

Figure 3. The influence of common activation on the additive criterion. The color legend is described in Figure 1. The white bars indicate common activation. S_1+S_2 is the sum of the activation produced with S_1 and S_2.

Figure 4. The influence of baseline on the additive criterion. Hemodynamic response curves for simulated events with stimulus modalities S_1, S_2 and S_{12} for event-related designs with fixed ISIs of 12 s (A), variable ISIs with a mean of 9 s (B), and variable ISIs with a mean of 6 s (C). Observed data in bar graphs show mean BOLD activation calculated as the area under the curve in a time window from 3-7 s post-stimulus onset. True data are the same, but calculated from the true underlying distribution of BOLD activation values. Baseline effect bar graphs relate the true data to the observed data by estimating the shift in baseline due to overlap of successive HRFs.

Figure 5. A null hypothesis for assessing neuronal convergence. Symbols in (B) and (C) are described in Figure 1, except that stimuli are presented in high (H) and low (L) quality versions. The graph in (A) illustrates differences between high and low conditions calculated from (B).

Figure 6. The relationship between inverse effectiveness and the additive-differences criterion. Legend and symbols are described in Figures 2 and 5. Single-unit activity as a function of stimulus modality and stimulus quality in multisensory neurons showing inverse effectiveness is shown in (A). The same activity organized to highlight the differences between high- and low-quality conditions is shown in (B). BOLD activation, shown in (C), is based on a model of three pools of neurons, two unisensory and one multisensory. The same activation organized to highlight the differences between high- and low-quality conditions is shown in (D). Differences in BOLD activation between high- and low-quality conditions as a function of stimulus modality are shown in (E).

Figure 7. Empirical data from two multisensory experiments. The results in (A) are differences in BOLD activation in multisensory superior temporal cortex (mSTC) for audio (A), visual (V), and AV stimulus modalities. These differences are calculated from the raw data shown in (B), which includes high- and low-quality stimulus conditions. The results in (C) and (D) are from the lateral occipital tactile visual area (LOtv) and are for visual (V), haptic (H), and VH stimulus conditions. Differences for this experiment were calculated across low and high stimulus similarity.

Figure 8. A nomenclature for additive-differences outcomes. Legend and symbols are described in Figure 5.

Figure 1

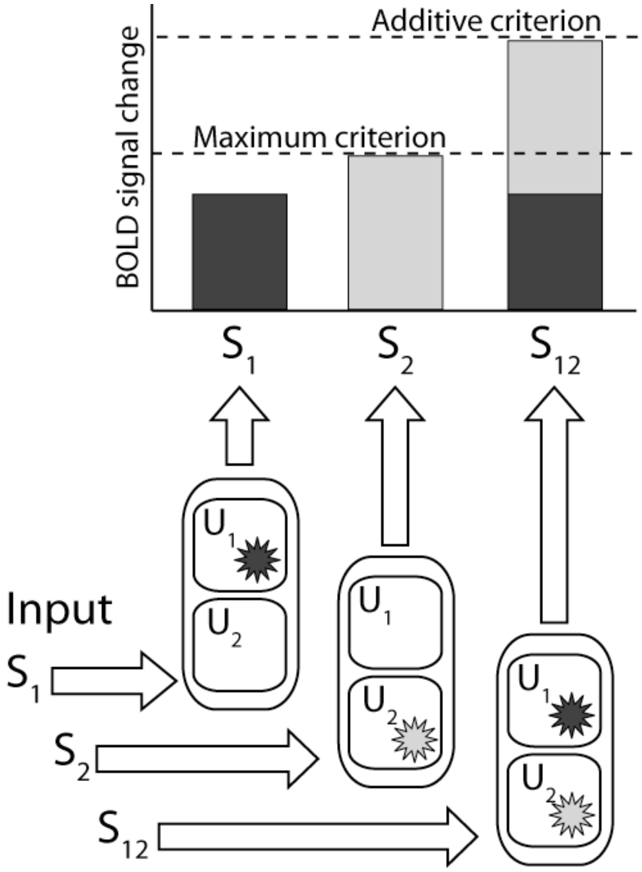

Additive criterion
Maximum criterion
BOLD signal change
S_1
S_2
S_{12}
U_1
U_2
Input
S_1
S_2
S_{12}

Figure 2

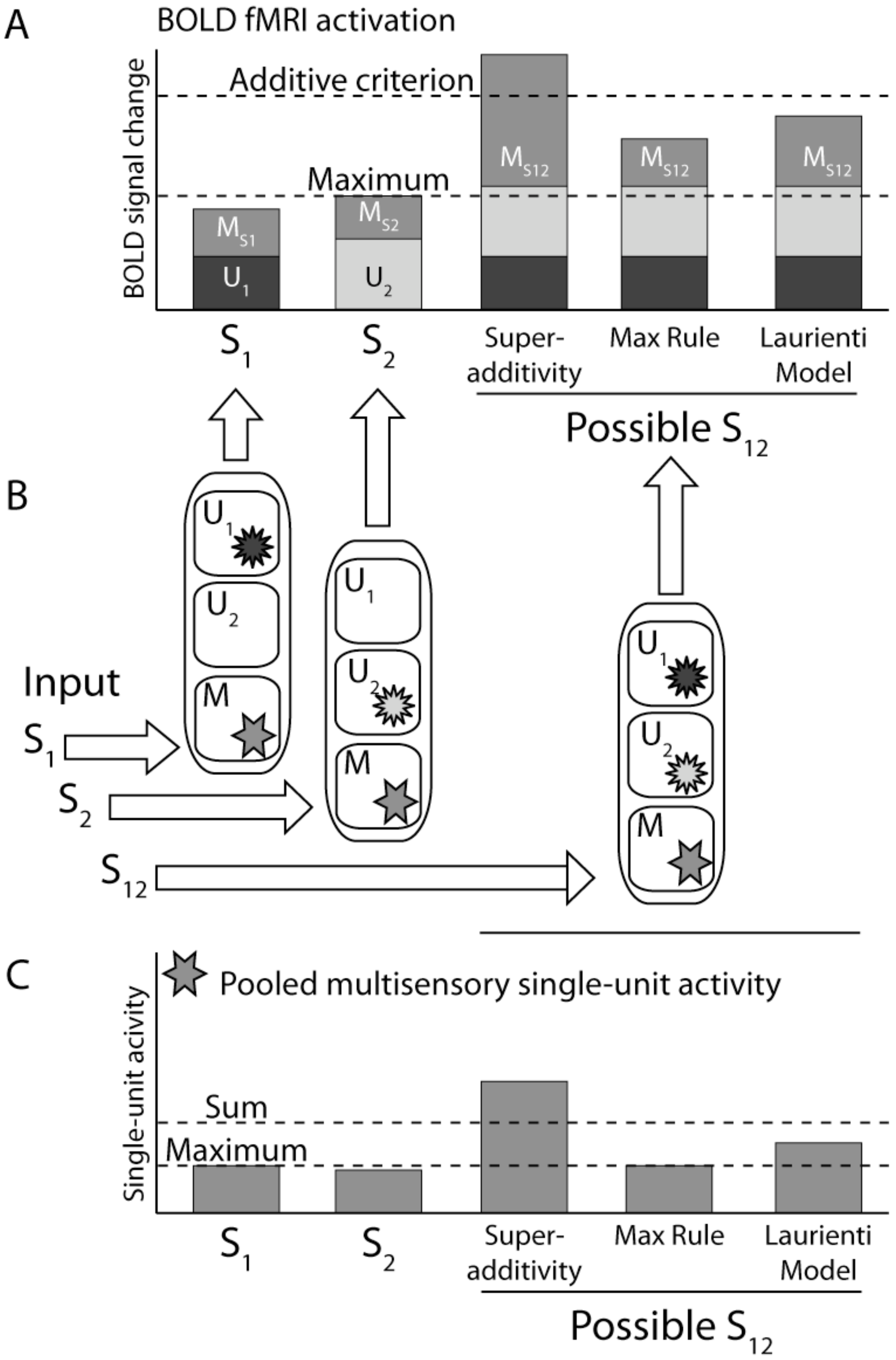
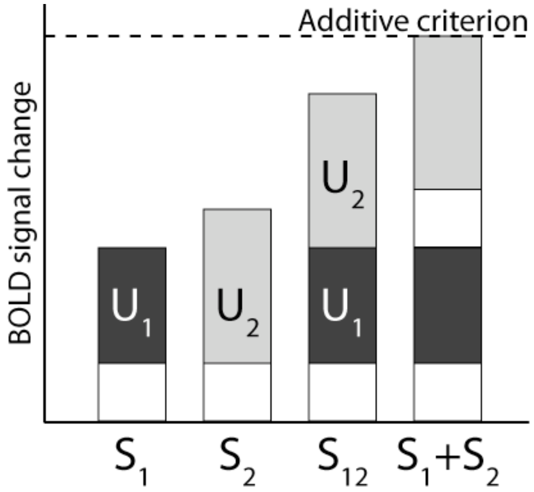

A
BOLD fMRI activation
BOLD signal change
Additive criterion
Maximum
M_S1
U_1
M_S2
U_2
M_S12
M_S12
M_S12
S_1
S_2
Super-additivity
Max Rule
Laurienti Model
Possible S_12
B
U_1
U_2
M
U_1
U_2
M
U_1
U_2
M
Input
S_1
S_2
S_12
C
Pooled multisensory single-unit activity
Single-unit activity
Sum
Maximum
S_1
S_2
Super-additivity
Max Rule
Laurienti Model
Possible S_12

Figure 3



Additive criterion
BOLD signal change
U_1
U_2
U_2
U_1
S_1
S_2
S_{12}
S_1+S_2

Figure 4

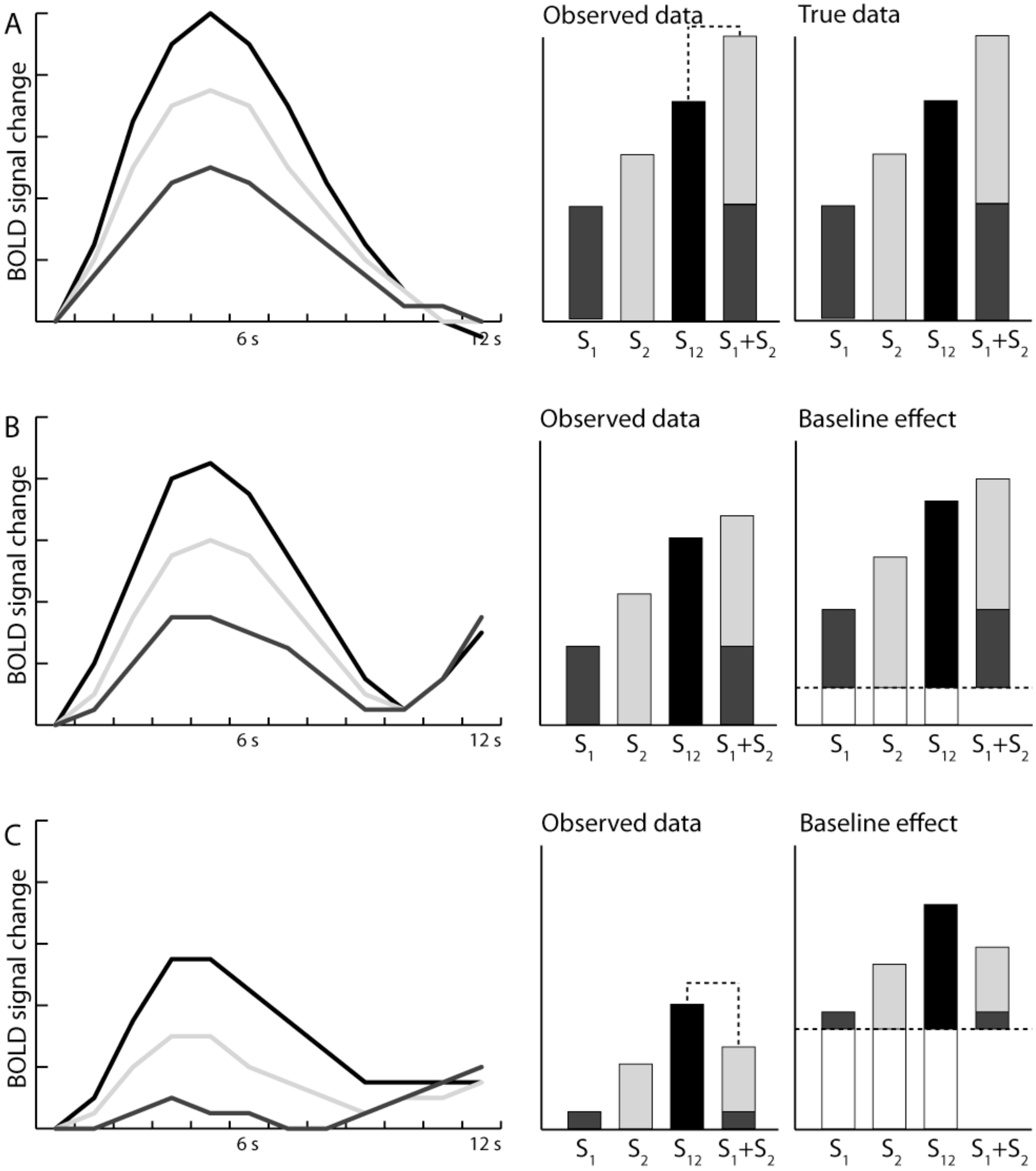

A
BOLD signal change
6 s
12 s
Observed data
True data
S_1
S_2
S_{12}
S_1+S_2
B
BOLD signal change
6 s
12 s
Observed data
Baseline effect
S_1
S_2
S_{12}
S_1+S_2
C
BOLD signal change
6 s
12 s
Observed data
Baseline effect
S_1
S_2
S_{12}
S_1+S_2

Figure 5

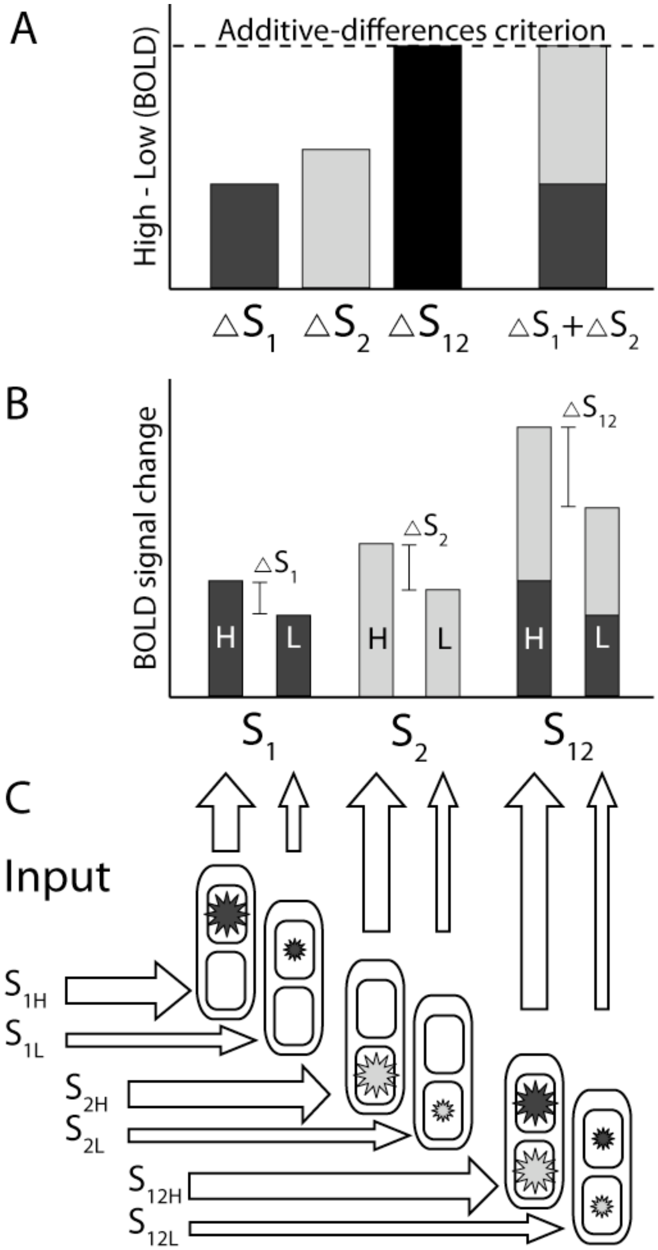

A
Additive-differences criterion
High - Low (BOLD)
△S1
△S2
△S12
△S1+△S2
B
BOLD signal change
△S1
△S2
△S12
H
L
H
L
H
L
S1
S2
S12
C
Input
S1H
S1L
S2H
S2L
S12H
S12L

Figure 6

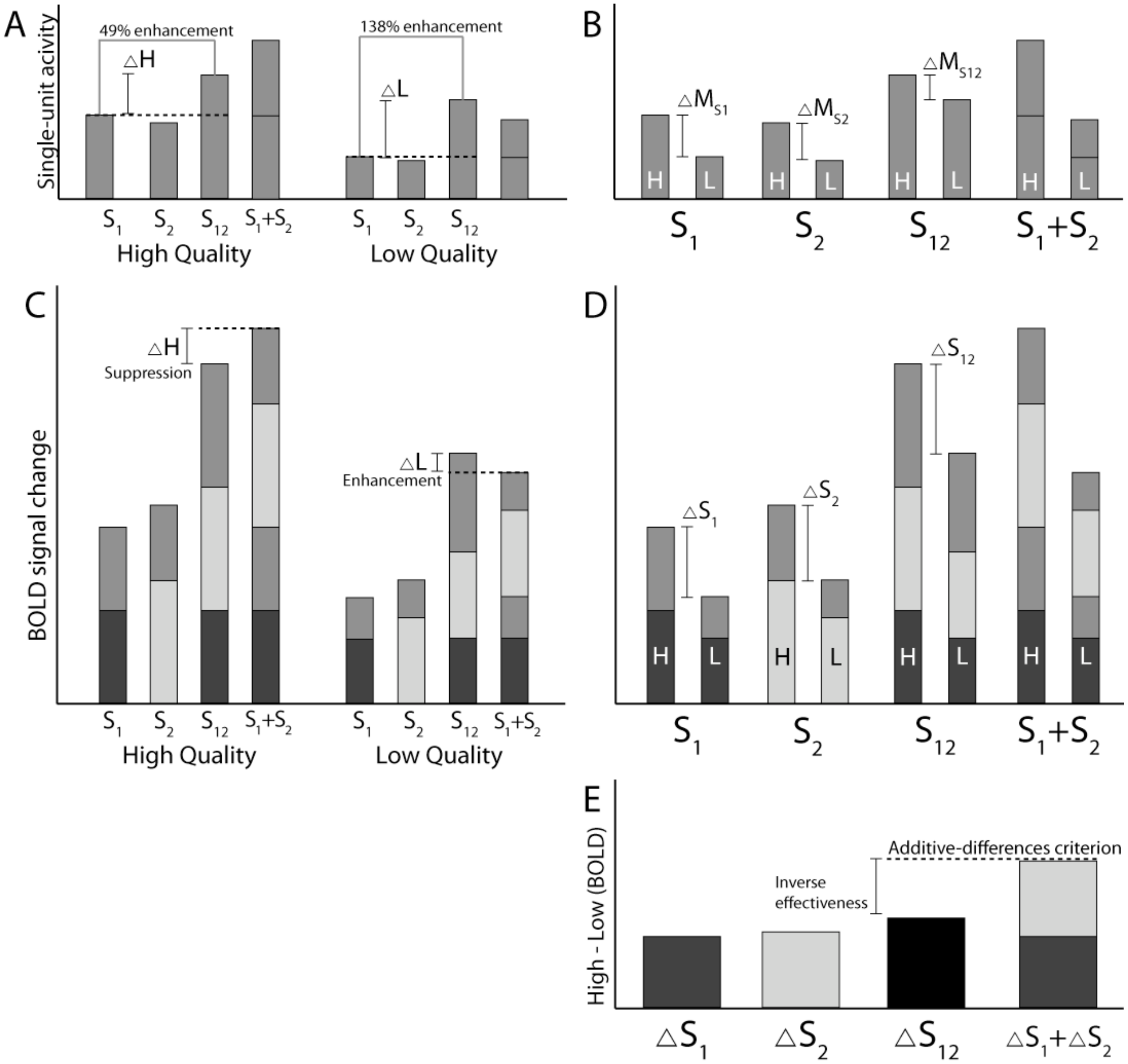

A
Single-unit acivity
49% enhancement
△H
138% enhancement
△L
S1
S2
S12
S1+S2
High Quality
S1
S2
S12
Low Quality
B
△MS1
△MS2
△MS12
H
L
S1
S2
S12
S1+S2
C
BOLD signal change
△H
Suppression
△L
Enhancement
High Quality
Low Quality
D
△S1
△S2
△S12
E
High - Low (BOLD)
Additive-differences criterion
Inverse effectiveness
△S1
△S2
△S12
△S1+△S2

Figure 7

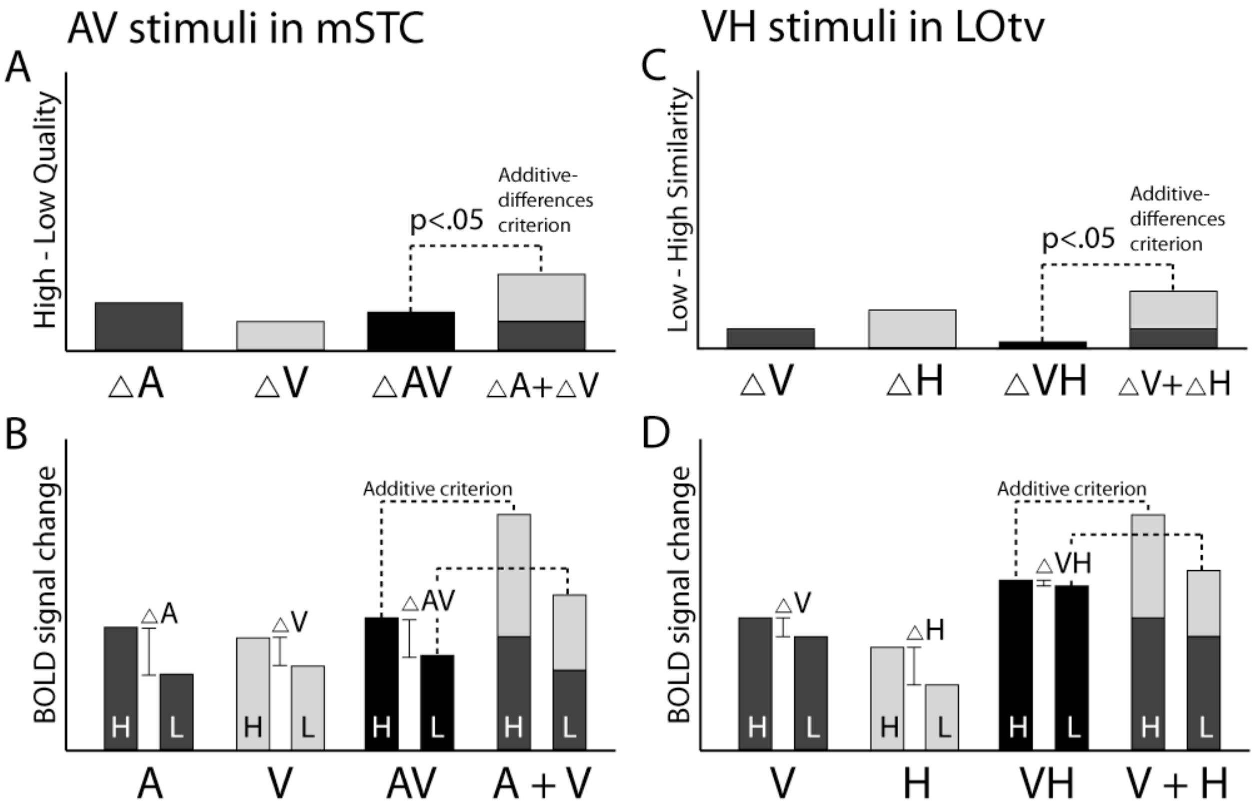
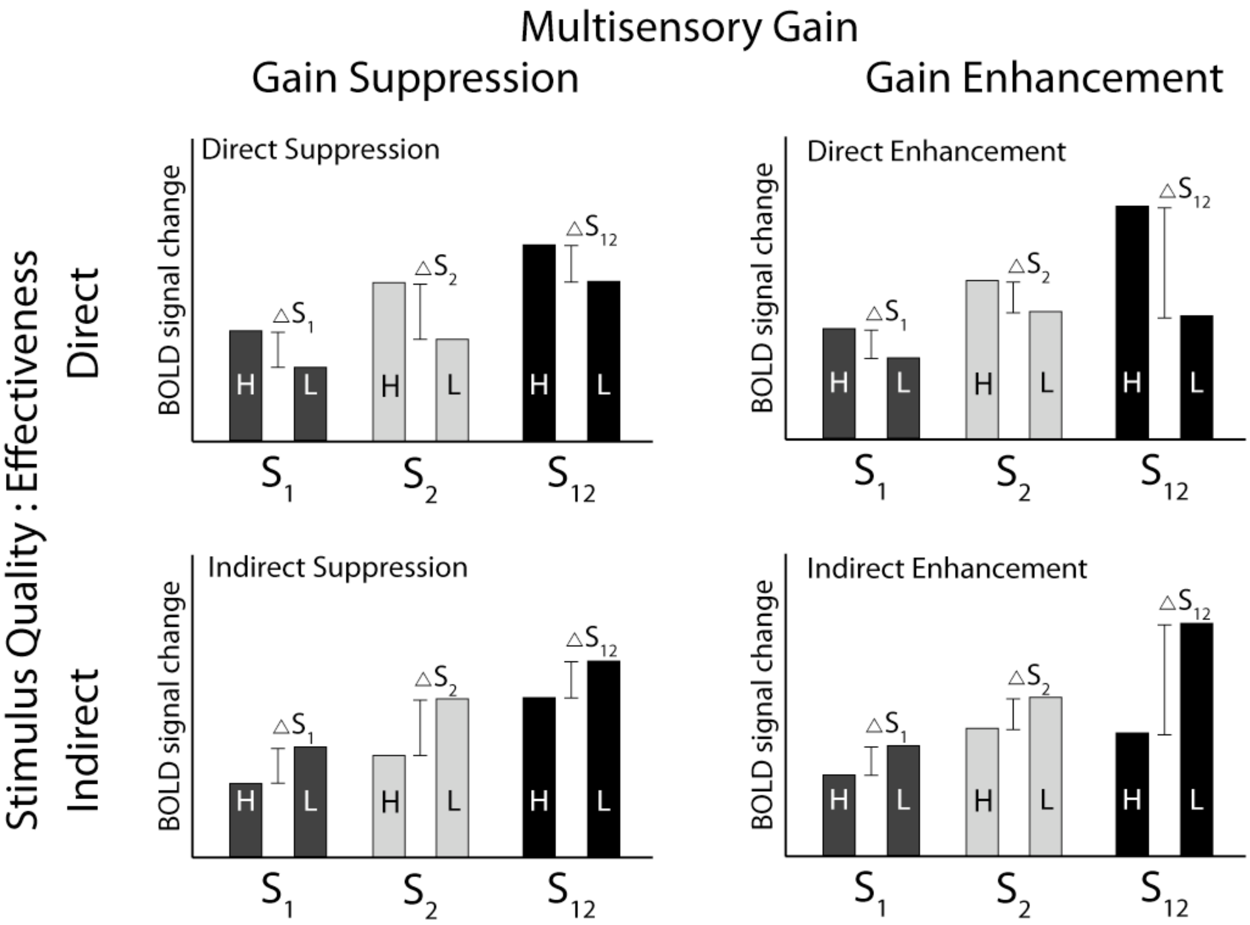

AV stimuli in mSTC
VH stimuli in LOtv
A
High - Low Quality
p<.05
Additive-differences criterion
△A
△V
△AV
△A+△V
B
BOLD signal change
Additive criterion
△A
△V
△AV
H
L
A
V
AV
A + V
C
Low - High Similarity
p<.05
Additive-differences criterion
△V
△H
△VH
△V+△H
D
BOLD signal change
Additive criterion
△V
△H
△VH
V
H
VH
V + H

Figure 8


Multisensory Gain
Gain Suppression
Gain Enhancement
Stimulus Quality : Effectiveness
Direct
Indirect
Direct Suppression
Direct Enhancement
Indirect Suppression
Indirect Enhancement
BOLD signal change
H
L
△S1
△S2
△S12
S1
S2
S12