Stimulus Rate Determines Regional Brain Blood Flow in Striate Cortex

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Intravenous bolus administration of oxygen 15–labeled water and positron emission tomography were used to measure changes in brain blood flow induced by two modes of photic stimuli over a wide range of repetition rates. These stimuli (patterned-flash and reversing checkerboard) were chosen in order to determine whether stimulus luminance or stimulus frequency was responsible for previously observed increases in blood flow in the striate cortex during photic stimulation. The response curves of blood flow change as a function of stimulus rate were nearly identical for both stimuli. These results suggest that elementary stimulus variables, such as repetition rate, can have a major effect on local cerebral responses, as measured with positron emission tomography and other radiotracer methods.

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Positron emission tomography (PET) provides quantitative measurements of regional cerebral blood flow (rCBF) and of the regional cerebral metabolic rate (rCMR) of oxygen ($rCMRO_2$) or glucose (rCMRGlc) in the human brain [4]. Under normal physiological conditions both these measurements closely reflect the regional rate of neuronal activity [1, 10]. This correla-

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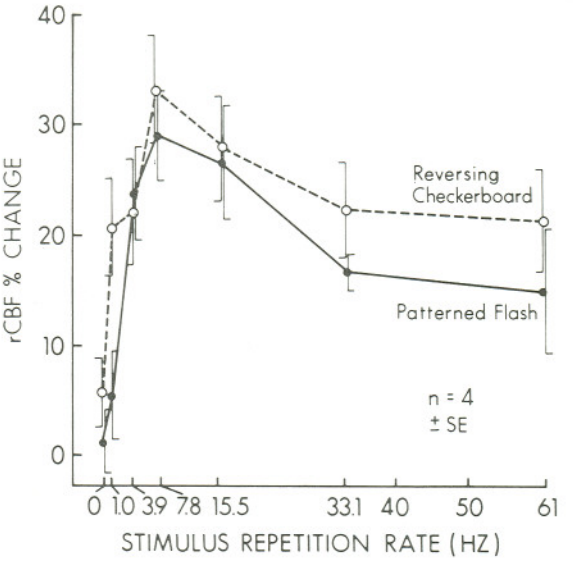
tion between neuronal function and rCBF and rCMR underlies the extensive use of positron and single-photon emission imaging for functional–anatomical mapping of the brain [1, 3, 4, 6–8]. The paradigms employed in such studies have been diverse and often quite complex, involving language, music, cognition, and motor performance. Although it has been maintained that elementary stimulus variables, such as rate and intensity, have no effect on cortical responses to activation paradigms [7], this question has not been directly addressed. Increases in striate cortex rCMRGlc induced by a diverse group of stimuli, ranging from white light to a park scene viewed through a window, were reported by Phelps and co-workers [3]. Although a positive correlation between stimulus "complexity" and metabolic response was reported, the stimulus variables responsible for this graded increase are unclear.

We recently reported a stimulus rate dependence of rCBF in human striate cortex [1]. Because the stimulus employed was a repetitive flash, however, the luminance averaged over the scanning interval was linearly related to the stimulus rate. Thus, the rCBF responses demonstrated in that study correlated with both rate and luminance. To determine whether the observed response function was induced by variation in rate or in luminance, a comparison between a repetitive constant-luminance stimulus and a repetitive flash stimulus was made and is the subject of this report.

Methods

rCBF was measured with the PETT VI system [9] and an intravenously administered bolus of oxygen 15–labeled water [2, 5]. Eight CBF measurements were made during each scanning session at intervals of 10 to 15 minutes in the manner previously described [1]. Four normal volunteers, 2 male and 2 female, took part. Each subject underwent two complete scanning sessions within three weeks. During one scanning session patterned-flash stimuli (luminance varying with rate) were presented with a pair of lightproof goggles, each containing a 1.5 cm × 1.5 cm rectilinear matrix of thirty 0.2 cm–diameter light-emitting diode dots (Model S10VS; Grass Instruments). The position of the eye pieces was adjusted to give a single binocular, foveally centered image, subtending approximately 45 degrees of arc. During the other session, visual stimuli were presented with a miniature, black-red reversing checkerboard (luminance constant at all rates; Model S10VS; Grass Instruments) positioned 25 cm from the eye. The checkerboard contained thirty-six 1 cm checks and subtended 13.5 degrees. Both stimulators delivered square-wave pulses of monochromatic light at 6,400 Å (goggles) or 6,260 Å (checkerboard). The initial and final scans of each series of eight were done without visual stimulation. During the intervening six scans, visual stimulation was given, beginning 60 seconds prior to scan initiation. The stimulus rate was varied from scan to scan in random order, with each subject receiving stimuli at 1.0, 3.9, 7.8, 15.5, 33.1, and 61 Hz. For the patterned-flash stimuli, the duration (5 ms) and intensity of each flash were constant, making luminance averaged over the 40-second scanning interval a linear function of stimulus rate. The reversing checkerboard stimuli maintained constant luminance regardless of stimulus rate.

Regional striate cortex CBF responses to stimulation, expressed as the percentage of change in rCBF (rCBF%△) from the initial unstimulated scan, were computed in a manner described in detail elsewhere [1].



Local blood flow response in striate cortex as a function of stimulus repetition rate. Blood flow in striate cortex varied systematically with stimulus rate. Maximum response occurred at 7.8 Hz (in four of four checkerboard studies and three of four patterned-flash studies) or at 15.5 Hz. The response curves are nearly identical with respect to rate, despite other differences between the two stimulus modalities. Regional cerebral blood flow (rCBF) changes are expressed as the percentage of change in rCBF (rCBF%△) from the initial unstimulated scan. Each point represents the mean rCBF%△ at that stimulus rate. The error bars indicate ± 1 SE about the mean. Note that the rCBF%△ for 0 Hz is the percentage of change evident in the final unstimulated scan from the initial unstimulated scan, demonstrating the minimal residual effect on rCBF of the preceding six episodes of visual stimulation. The same 4 subjects were used for both protocols. The method of head alignment, stabilization, and position recording [1] assured that the plane of each tomographic slice was constant throughout the sixteen scans obtained from each subject. For an individual subject all measurements were taken from precisely the same brain region.

Results

Visual stimulation induced marked, local increases in blood flow in the striate cortex. For every subject, regional blood flow in the striate cortex varied systematically with stimulus rate during both patterned-flash and checkerboard stimulation. The response curves of local blood flow change as a function of stimulus rate (Figure) demonstrate the near identity of the regional

responses, despite differences between the two stimulus modalities in luminance, pattern, distance from the retina, and degrees subtended in the visual field. Maximal rCBF response occurred at 7.8 Hz with each stimulus.

Discussion

This study demonstrates that stimulus rate directly determines the rCBF response within the striate cortex to repetitive photic stimulation.

The response function described, rCBF%△ as a function of stimulus rate, is necessarily influenced by the method of measurement employed (PET). Radiotracer techniques for measuring physiological variables in brain require the accumulation of tissue counts over a finite time, 40 seconds for our method [2, 5] and approximately 45 minutes for techniques involving deoxyglucose [4]. If a relatively uniform neuronal response accompanies each stimulus repetition, the stimulus rate will directly affect both the mean neuronal activity integrated over the measurement interval, and measurements of rCBF or rCMR. Thus, a relationship between stimulus rate and rCMR would be anticipated and has been established in the peripheral nervous system and in subcortical structures in the central nervous system of rats [10]. Similarly, blood flow in human striate cortex increases linearly between 0 and 7.8 Hz [1], presumably on the same basis. Beyond a critical frequency, however, the response functions cease to be linear, plateauing or even falling as rate increases [1, 10]. This nonlinearity implies that the neuronal response following each stimulus repetition is not uniform at all stimulus rates [1]. Thus, the response function of rCBF%△ versus rate is influenced by both the response characteristics of the neural system being activated and the methodological necessity of accumulating tissue counts over an interval of time.

The dependence of rCBF on stimulus rate demonstrated here has widespread implications. Investigators using radiotracer methods to study local brain responses should consider the potential effect of rate on responses in any neural system. The absolute magnitude of a local response can be a function of rate, as we have shown. Thus, repetition rate must be known and controlled for when responses involving unlike stimuli or performance tasks are compared. If not, ambiguity will remain as to whether response differences between unlike conditions are due to rate or to other task variables. For example, the response function of rCMRGlc versus complexity described by Phelps and colleagues [3] may be due to differences in the delivery rate of the steady stimulus, the 2 Hz checkerboard, and the rapidly changing park scene. Similarly, the degree of activation of supplementary motor cortex during motor performance tasks has been related to the complexity of the tasks [8]; the simple, repetitive task was much slower (1.0 movements per second) than was the complex, sequential task (3.2 movements per second), however. Finally, the finding that the anticipation of a tactile stimulus induced a greater rCBF response (25%) in the postcentral gyrus than did 1 Hz electrocutaneous stimulation (13%) may simply indicate that a suboptimal rate was chosen for delivery of the electrocutaneous stimulus [7]. We have found that the somatosensory system is highly sensitive to stimulus rate, with massive rCBF increases (more than 50%) occurring in the postcentral gyrus at certain vibratory frequencies (unpublished data, 1984).

We suggest that complex performance tasks such as those involving language, music, and cognitive processing introduce numerous variables whose impact upon measurements of rCBF and rCMR is unknown. Rate is one such variable. The effect on rCBF and rCMR of other stimulus variables, including intensity, duration, and pattern, must also be defined to enable more complex activation paradigms to be properly designed, executed, and interpreted.

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