A change detection approach to study visual working memory of the macaque monkey

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A core aspect of working memory is that only a limited amount of information can be held at one time, but the investigations of its underlying neural mechanisms in animal models have been dominated by paradigms requiring the retention of a single memorandum. In humans, the information processing limitations of visual working memory have been studied extensively using a sequential comparison procedure, in which subjects detect a change in a multiple-item array following a retention interval. Here, we adopted this approach to study the working memory ability of the macaque monkey. We trained two female rhesus monkeys (*Macaca mulatta*) to perform a change detection task, in which they were required to report with a saccadic eye movement which one of several items (two to five colored stimuli) in a array had changed color after a 1-s retention interval. Performance gradually declined as a function of set size but always exceeded chance probability. These results show that monkeys possess sufficient information processing capability to perform a visual working memory task requiring the simultaneous maintenance of mnemonic representations of multiple items and validate this animal model for investigation of the neural mechanisms underlying the temporary retention of more than one memorandum.

Keywords: visual working memory, short-term memory, mnemonic processes, executive function, sequential comparison, change detection, monkey

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Introduction

Working memory is a cognitive process that allows temporary retention of information for the guidance of forthcoming behavior (Baddeley, 1992; Goldman-Rakic, 1990). The neural basis of working memory has been investigated extensively in non-human primates with variants of the classical delayed response task (Hunter, 1913), such as the delayed matching-to-sample (Miller, Erickson, & Desimone, 1996; Miller, Li, & Desimone, 1991) and the memory-guided saccade tasks (Goldman-Rakic, 1995). Such studies have established a solid link between the cognitive process referred to as working memory and the neural events underlying performance on working memory tasks. Neuronal activity recordings have revealed persistent activity during the delay period following stimulus disappearance and preceding the motor response (Funahashi, Bruce, & Goldman-Rakic, 1989, 1991; Fuster, 1973; Fuster & Alexander, 1971; Gnadt & Andersen, 1988; Miller et al., 1996). Such activity has been identified as a putative neural substrate of the mnemonic process, because its properties bear a resemblance to the expected characteristics of mnemonic representations: it reflects the properties of sensory memoranda, such as spatial location (Funahashi et al., 1989, 1990, 1991; Gnadt & Andersen, 1988; Wilson, Scalaidhe, & Goldman-Rakic, 1993), item identity (Miller et al., 1996; Wilson et al., 1993), or both (Rainer, Asaad, & Miller, 1998). In the case of memory-guided saccades, this interpretation has been further supported by the observation of decreased persistent activity on error trials (Funahashi et al., 1989) and performance deficits following dopamine-related disruptions of persistent activity within the prefrontal cortex (Sawaguchi & Goldman-Rakic, 1994; see also Sawaguchi, 2001; Sawaguchi, Matsumura, & Kubota, 1988).

In addition to its transient nature, working memory is limited in the amount of information that can be retained at one time. Consequently, a substantial number of investigations in the human cognitive psychological literature have been dedicated to determining the number of items that can be simultaneously retained (Cowan, 2001; Daneman

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& Carpenter, 1980; Luck & Vogel, 1997; Miller, 1956; Milner, 1968; Sperling, 1960). In comparison to this rich body of behavioral work, the neural mechanisms underlying multiple-item working memory are poorly understood. Most investigations of the neural substrates of working memory using animal models have been carried out using tasks that require the retention of a single memorandum only. The few studies carried out to date have used tasks such as the self-ordered (Hasegawa, Blitz, & Goldberg, 2004; Kimble & Pribram, 1963; Petrides, 1991, 1995) or multiple object sequence tasks (Warden & Miller, 2007). While both undoubtedly require the use of mnemonic resources, their performance depends upon factors other than the number of items that must be retained. Multiple object sequence tasks require retention not only of the identity of individual memoranda but also of their order, while self-ordered tasks may access additional cognitive processes, such as inhibitory control, the ability to employ response strategies, and monitoring of self-generated responses (Collins, Roberts, Dias, Everitt, & Robbins, 1998; Levy & Goldman-Rakic, 1999). Thus, any variations in behavioral performance or neural activity observed in such tasks cannot be unambiguously attributed to the ability to retain multiple items within working memory.

An influential approach employed in the human cognitive psychological literature to determine the amount of information that can be simultaneously maintained within visual working memory has been the sequential comparison procedure. In sequential comparison tasks, observers report a change in an array of stimuli following a retention interval and memory load is varied by changing the number of items in the array (Cowan, 2001; Luck & Vogel, 1997; Pashler, 1988; Phillips, 1974; Vogel, Woodman, & Luck, 2001). From a neurobiological perspective, an advantageous aspect of this procedure is that memory load is easily manipulated and the concomitant variations in the mnemonic process are directly related to task performance. Thus, changes in neural activity observed during the delay period of this task are expected to reflect the mnemonic processes reflecting the representation of multiple items. Indeed, human studies have successfully employed this logic to investigate the neural basis of multiple-item working memory (Robitaille, Grimault, & Jolicoeur, 2009; Robitaille et al., 2010; Sauseng et al., 2009; Todd & Marois, 2004; Vogel & Machizawa, 2004; Xu & Chun, 2006).

A comprehensive understanding of working memory requires extension of the highly successful approach used to study the neural mechanisms of working memory for single memoranda in non-human primates (see, for a review, Goldman-Rakic, 1995). Toward establishing an animal model, we trained rhesus monkeys to perform a sequential color change detection task similar to that employed in human studies (Luck & Vogel, 1997) to determine their visual working memory ability and the influence of memory load on their performance.

A preliminary report of these data has previously been presented in abstract form (Heyselaar, Johnston, & Paré, 2009).

Methods

Subjects and apparatus

Data were collected from two female rhesus monkeys (*Macaca mulatta,* 5.0–6.0 kg, 10–11 years old) cared for and used under experimental protocols approved by Queen's University Animal Care Committee and in accordance with the Canadian Council on Animal Care guidelines. Animals were prepared for experiments by undergoing a surgery, in which a head restraint and subconjunctival search coils for monitoring eye position were implanted (see, for details, Shen & Paré, 2006). Monkeys were housed in large enclosures (Clarence, Scott, Dorris, & Paré, 2006) and received both antibiotics and analgesic medications during the post-surgery recovery period, after which they were trained with operant conditioning and positive reinforcement to perform fixation and saccade tasks for a liquid reward until satiation.

Behavioral paradigms, visual displays, and data acquisition were controlled using the QNX Real-Time Experimentation Software (REX) system (Hays, Richmond, & Optican, 1982). Visual stimuli were generated by a display program using Matlab and the Psychophysics Toolbox (Brainard, 1997) running on a Power Mac G4 computer and presented on a 37″ monitor (NEC MultiSync XP37 plus, 60-Hz non-interlaced, 800 × 600 resolution, 32-bit color depth) at a viewing distance of 57 cm.

Stimulus arrays consisted of sets of two to five colored squares, each measuring 1.2° × 1.2°, presented at an eccentricity of 10° from a central fixation spot. For each set size, the spatial configuration of the stimuli remained identical across trials. For set size two, stimuli were on the right and left sides of the fixation spot. For set size three to five, stimuli were arranged equidistantly from each other with one stimulus located directly above the fixation spot. Although the distance between adjacent stimuli varied with set size, we estimated that crowding effect was not a significant factor in these experiments. Studies of crowding (Bouma, 1970; Pelli, Palomares, & Majaj, 2004) have shown that the area over which visual stimuli interact scales roughly with their eccentricity by a factor of 0.5 (area = 0.5 × eccentricity). For our stimulus displays, in which stimuli were presented at an eccentricity of 10°, the area of interaction can, therefore, be estimated to be 5°, a value substantially less than the 12° that separated the stimuli at the largest set size we tested.

The color of each stimulus was chosen randomly from a predetermined library of six colors highly discriminable from each other: red (CIE $x = 0.633$, $y = 0.327$, $L = 8.9$ cd/m^2), green (CIE $x = 0.288$, $y = 0.602$, $L = 7.25$ cd/m^2),

blue (CIE x = 0.15, y = 0.06, L = 9.82 cd/m^2), magenta (CIE x = 0. 257, y = 0. 121, L = 9.38 cd/m^2), yellow (CIE x = 0.416, y = 0.501, L = 7.05 cd/m^2), or cyan (CIE x = 0.237, y = 0.393, L = 7.43 cd/m^2), with the restriction that a given color could appear only once in each array. Luminance and chromaticity were measured using a Minolta CA100-Plus photometer.

Behavioral paradigms

Monkeys performed a color change detection task similar to that employed in human studies of working memory (Figure 1). Each trial began with the presentation of a small (0.5°) white fixation spot (CIE x = 0.30, y = 0.289, L = 10.2 cd/m^2) at the center of the display monitor. Animals were required to fixate this spot within 1000 ms of its appearance and maintain fixation within a 2° × 2° window for 500–800 ms. While they maintained fixation, a memory array composed of a randomly determined set of two to five stimuli was presented for 500 ms. Offset of the memory array was followed by a 1000-ms retention interval, in which the display screen was blank with the exception of the central fixation spot. The duration of the retention interval was chosen to correspond with that of change detection tasks used in human studies (Alvarez & Cavanagh, 2004; Awh, Barton, & Vogel, 2007; Luck & Vogel, 1997; Vogel & Machizawa, 2004). At the end of the retention interval, monkeys were presented with a test array consisting of the same number and spatial configuration of stimuli as in the memory array but with the color of one stimulus changed. Coincident with this, the fixation spot was dimmed (L = 1.37 cd/m^2) and monkeys were required to make a saccade to the location of the changed stimulus within 500 ms to obtain a liquid reward. This task capitalizes on the highly developed ability of monkeys to recognize a novel stimulus (Mishkin & Delacour, 1975). The monitor screen was illuminated with diffuse white light (1.5 cd/m^2) during the inter-trial interval (1000–1500 ms) to prevent dark adaptation.

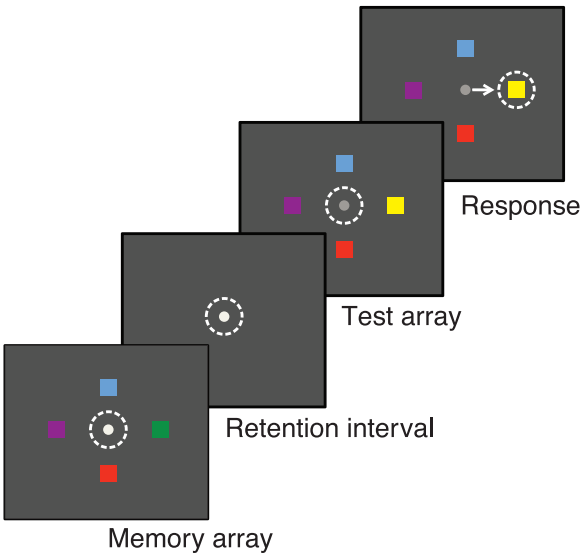

Figure 1. Depiction of a correctly performed trial in the color change detection task. Dotted circle and arrow represent current eye position and the saccade response.

Training included sessions in which the animals performed trials with a color change randomly interleaved with an equal proportion of trials with no color change. On these no change trials, the sequence and timing of trial events were the same as change trials, with the exception that the memory and test arrays were identical, and animals were required to indicate the absence of a color change by maintaining fixation on the central fixation spot for 600 ms following onset of the test array. These sessions were conducted at a fixed set size of two items.

Data analysis

To assess performance, we computed the proportion of correct responses and measured the latency of these responses, defined as the time between the onset of the test array and saccade initiation.

As an additional index of performance, and to transform our data to a scale comparable to that obtained in human studies using yes/no change detection tasks, we used a signal detection approach to derive a measure of detectability (d') from the proportion of correct responses made by each animal at each set size. We adopted this approach based on the logic that our change detection task could be considered as a spatial m-alternative forced-choice (m-AFC) task in which m is equal to set size (2, 3, 4, or 5), and the observer must choose which of the m locations contains a signal on every trial; the relevant signal in this case being a color change. This method is based on the established relationships between d' and proportion correct for yes/no detection and forced-choice procedures as well as the area theorem, which states that the probability of a correct response obtained in 2-AFC tasks is equal to the area under the Receiver Operating Characteristic (ROC) curve obtained in yes/no detection tasks (Macmillan & Creelman, 2005; Wickens, 2002) and assumes that the observer operates by an equal-variance Gaussian model and has no location bias. The logic of this procedure is described briefly below.

The probability of a correct response on a given trial in a spatial m-AFC task is the probability that a given value of the signal (X_s), present at one location, exceeds the maximum of the noise values present at the other spatial locations (X_n). For a specified value of X_s, x, this may be denoted as the following conditional probability:

$$P(\text{correct}\,|\,X_s = x) = P[\max(X_{n1}, X_{n2,\ldots Xn,m-1}) < x], \quad (1)$$

which may be alternatively written as $F_n^{m-1}(x)$, where $F_n(x)$ is the cumulative distribution function. The unconditional probability of a correct response may be obtained by averaging these values over the distribution of signal events:

$$P_{\text{correct}} = \int_{-\infty}^{\infty} F_n^{m-1}(x) f_s(x) dx. \quad (2)$$

Thus, P_{correct} is the average probability that the signal exceeds all noise observations, computed over the distribution of signal values. Using these equations, it is possible to compute the correct response probabilities for any specified distributions of X_s and X_n and thus d' for any m number of alternatives. In this manner, the proportion of correct responses corresponding to given values of d' may be computed for a task with any m alternatives. We obtained values of d' from tables of d' and P_{correct} for m alternatives presented by Hacker and Ratcliff (1979) using these calculations. This procedure is described in detail by Wickens (2002).

Results

Both animals received extensive training on the color change detection task (*monkey B,* 47 sessions; *monkey G,* 99 sessions). The main data for this report were collected in ten consecutive experimental sessions that followed the initial training period in which the animals performed at least 600 trials. This consisted of a total of 9141 and 9656 trials for *monkeys B* and *G,* respectively. Mean and individual session proportion correct responses are shown as a

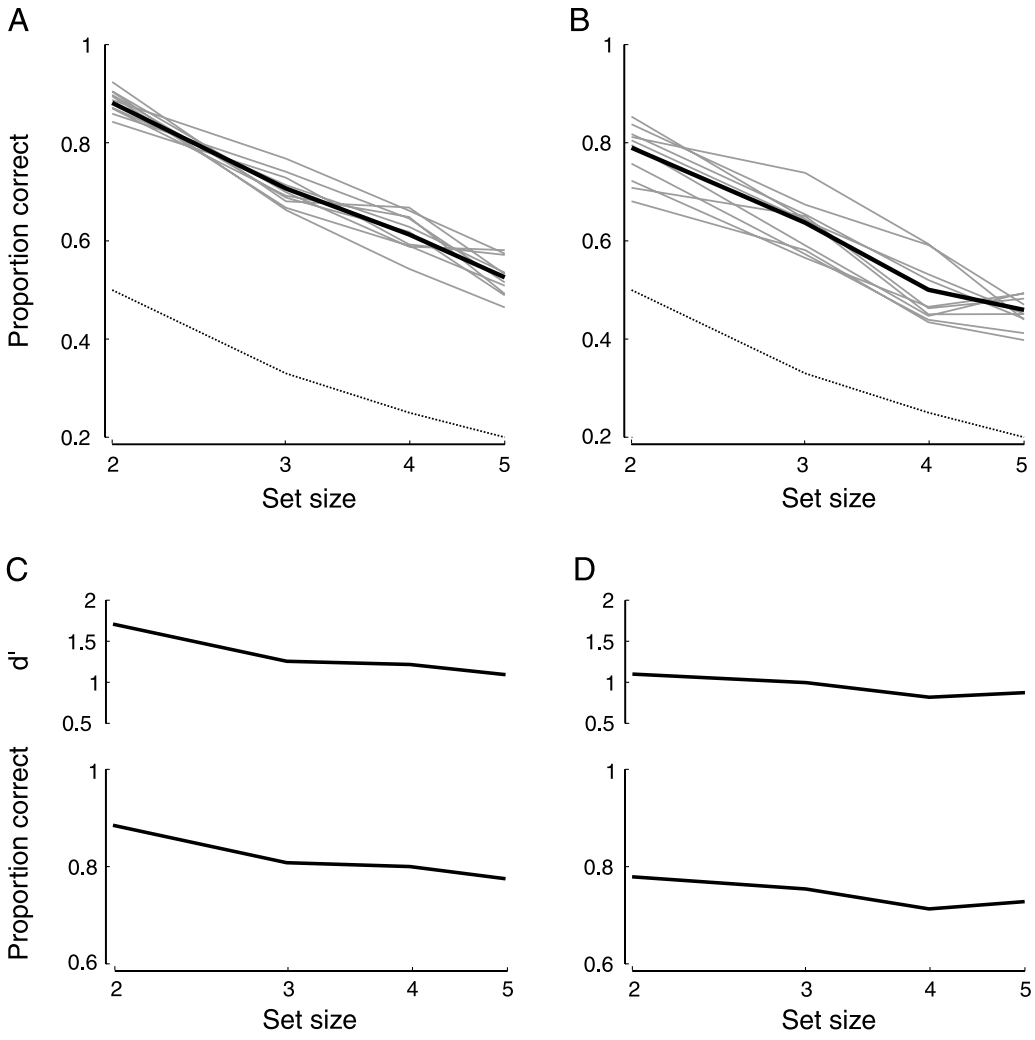

Figure 2. Proportion correct, estimated d' values, and estimated yes/no proportion correct as a function of set size. (A, B) Proportion of correct responses in the color change detection task as a function of set size for *monkeys B* and *G,* respectively. Dashed lines represent chance performance (1/set size). (C, D) Estimated d' values (top panels) and yes/no proportion correct (bottom panels) as a function of set size for *monkeys B* and *G*.

function of set size in Figure 2. For *monkey B,* proportion correct averaged 0.89, 0.70, 0.62, and 0.53 at set sizes two to five, respectively (Figure 2A). For *monkey G,* these figures were 0.78, 0.63, 0.49, and 0.45 (Figure 2B). These proportions exceeded chance probability at all set sizes (0.5, 0.33, 0.25, and 0.2) for both animals (z-test, $p < 0.05$), and they significantly decreased as a function of set size (ANOVA, $p < 0.0001$). Mean values of d' followed a similar decreasing trend, ranging from 1.71 to 1.09 from set sizes two to five for *monkey B* and from 1.10 to 0.87 for *monkey G* (Figures 2C and 2D). Based on the signal detection theory logic described in the Methods section, the mean proportions correct in a yes/no task corresponding to these values of d' are 0.89, 0.81, 0.80, and 0.78 for *monkey B* at set sizes two to five and 0.78, 0.75, 0.71, and 0.73 for *monkey G* (Figures 2C and 2D).

The assumption made when making inferences regarding mnemonic processes from change detection performance is that the latter is an outcome of the process of comparing stimuli in the test array with mnemonic representations of those presented in the memory array. Specifically, we predicted that if animals were using mnemonic processes, their incorrect responses could be classified as "diligent guesses" (Link, 1982) made on the basis of mnemonic information rather than random responses to a given location made in the absence of such information. The logic of diligent guessing predicts that the latency of the animals' incorrect responses should be equal or greater than that of correct responses since both outcomes result from the same deliberative process. The response latency distributions of both animals (Figure 3) are consistent with this assertion. The difference between the latency of correct and incorrect responses was tested for each animal with a two-way ANOVA, with set size (two to five) and trial type (correct vs. error) as factors. *Monkey B* exhibited a significant interaction ($p < 0.05$), and post-hoc comparisons showed that latency was significantly greater on error trials at all set sizes (mean latency: 221 vs. 207 ms; t-test, $p < 0.05$). No significant effect of trial type or interaction was found in *monkey G* (mean latency: 182 vs. 180 ms; ANOVA, $p = 0.313$ and 0.273, respectively). These effects were consistent across single experimental sessions for both animals. Latencies for incorrect trials significantly exceeded those of correct trials in all ten sessions for *monkey B* (ANOVA, $p < 0.05$). For *monkey G,* no significant differences were observed, with the exception of three sessions in which latencies of incorrect trials exceeded that of correct trials. No increases in reaction time as a function of set size were found for either animal in any session.

To ensure that the animals maximized the use of their mnemonic resources to perform the change detection task, we included in their training sessions with interleaved color change and no change trials, in which they then had to respond by maintaining fixation (see Methods section). Responses in both change and no change trials should reflect the outcome of the same comparison process, and comparable performance in both types of trials is expected. Here we report data collected in a single experimental session that preceded the ten sessions from which data were presented above (586 and 582 trials for *monkeys B* and *G,* respectively). Both animals were as proficient in both types of trials as in the sessions with change trials only (hits: 0.77 and 0.68; correct rejections: 0.70 and 0.72 for *monkeys B* and *G,* respectively), making a significantly greater proportion of correct responses than errors (z-test for proportions, $p < 0.05$). These results are consistent with a mnemonic substrate for change detection performance, with the caveat that the required sensitivity and specificity of the detection in this version of the task necessitates the additional process of selecting one of two behavioral responses.

Based on results presented above, we assert that the performance of our animals in this change detection task is consonant with an ability to represent more than a single memorandum within working memory. An alternative interpretation is that their performance reflects a strategic process by which the animals retain in working memory only a single location or color. The animal would then respond correctly on trials in which the exact item retained

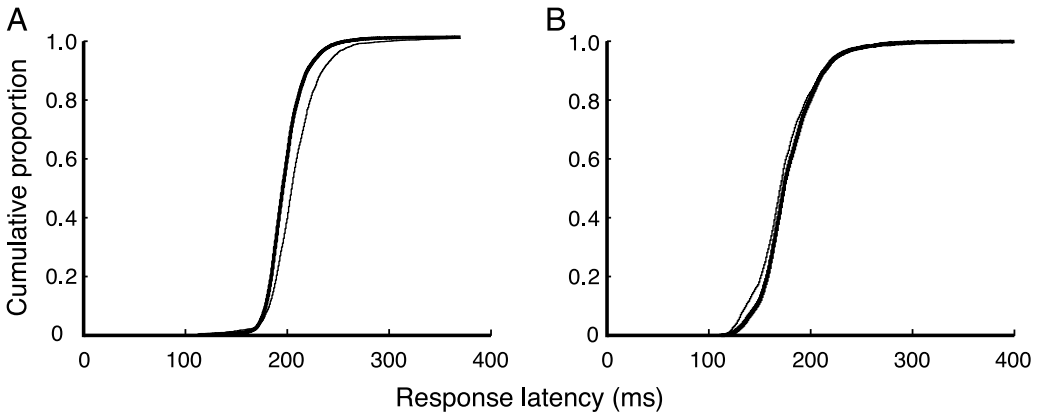

Figure 3. Cumulative latency distribution of correct (thick line) and incorrect responses (thin line) for (A) *monkey B* and (B) *monkey G*.

in memory had changed color but otherwise chose randomly among the remaining alternatives. First, we reasoned that such a strategy, if based on stimulus location, would be reflected in the proportion of correct responses directed to each of the stimulus locations within each set size. To examine this possibility, we contrasted the performance at the location for which the animal made the greatest proportion of correct responses in each session to the average performance at the alternative locations. For instance, the maximum performance ratio at set size five is 4 (1/0.25), when a single spatial location is perfectly tracked and performance is at chance for the alternative locations; the minimum ratio of 1 denotes evenly distributed responses. The ratios observed across sessions were significantly (t-test, $p < 0.001$) less than this predicted value (*monkey B*: mean, 1.60; range, 1.41–2.01; *monkey G*: mean, 1.68; range, 1.33–2.16). We obtained similar results for the other set sizes. Next, to test whether the animals retained a single color in working memory, we compared the performance predicted by such a strategy to that observed at each set size. We computed the predicted performance by determining the probability of one of the six colors appearing in arrays of each set size tested, the probability that a given color in the array would be the changed item, and the probability of an animal making a correct response under the assumption that they were memorizing a single color only. This logic predicted the following proportions of correct responses: 0.67, 0.50, 0.41, and 0.37 for set sizes two to five, respectively. These expected levels of performance were exceeded by both animals at all set sizes (z-test for proportions, $p < 0.05$), suggesting that implementation of such a strategy cannot fully account for the change detection performance of either animal. Performance on the control task (which included both change and no change trials) also exceeded that predicted based on either a spatial or a color strategy.

We also considered the possibility that the animals retained a single randomly chosen color or spatial location on a trial-by-trial basis. Under such a strategy, the overall probability of a correct response would be expected to equal the probability of a correct response, given that the chosen item changes color, multiplied by the probability that the chosen item changes color, plus the probability of a correct response given that the chosen item does not change, multiplied by the probability that the item does not change. This logic yielded predicted proportions correct of 1.0, 0.66, 0.50, and 0.40 for set sizes two to five, respectively. We found that the performance of both animals fell below the predicted value for set size two. However, the performance of *monkey B* significantly exceeded those predicted proportions correct at set sizes three, four, and five, while that of *monkey G* exceeded the predicted value at set size five (z-test for proportions, $p < 0.05$). Altogether, the results of these tests suggest that our animals were able to retain more than a single item within working memory, especially at the larger set sizes we tested.

Discussion

We implemented a color change detection task to study the visual working memory ability of the macaque monkey and how it is influenced by changes in memory load. Both monkeys showed change detection performance that declined gradually with increasing numbers of memoranda but remained well above chance. That their performance in this task reflected the use of mnemonic processes was evidenced by the animals' responses on error trials not being significantly shorter and by their ability to successfully perform an alternate version of the task that required the report of the contents of their working memory via one of two alternative responses. Our results demonstrate that macaque monkeys can simultaneously retain information regarding more than one item and are therefore suitable models to advance investigation of the neural mechanisms of mnemonic processes beyond the single memorandum. The information processing limits of human working memory have also been extensively investigated using color change detection tasks. Such studies have employed variations of the task in which observers report either whether a change has occurred (Awh et al., 2007; Luck & Vogel, 1997; Scolari, Vogel, & Awh, 2008; Vogel & Machizawa, 2004; Vogel, McCullough, & Machizawa, 2005; see, for a review, Vogel & Awh, 2008) or which item has changed (Gold et al., 2006; Hyun, Vogel, Woodman, Hollingworth, & Luck, 2009). Investigations using similar stimuli and set sizes to those we employed provide a useful point of comparison between the working memory performance of humans and our monkey subjects. Vogel et al. (2001) used stimulus arrays consisting of simple colored squares and a procedure in which trials with and without a color change were presented with equal probability. Observers reported whether a change or no change had occurred via a simple yes/no response. Similar to our results, they found that performance declined as a function of set size, with overall mean proportions correct of approximately 0.99, 0.96, and 0.89 for set sizes two to four and a predicted value of approximately 0.84 for set size five. These proportions are higher than those observed in our animals at all set sizes (0.84, 0.78, 0.76, and 0.76) when their performance levels were equated to proportion correct in a yes/no task using estimates of d' (Wickens, 2002). Hyun et al. (2009) used a color change detection task that closely matches the task that we implemented. Observers made a saccade to the location of the changed item following a retention interval for set sizes of two to four items. As with the results of yes/no designs, the performance of their human observers

declined as a function of set size and exceeded that of our animals, with proportions correct of approximately 0.93, 0.89, and 0.84 for set sizes two to four, as compared to the proportions of 0.83, 0.67, and 0.56 that we obtained. In sum, change detection performance reported for humans is generally higher than that of the monkeys we tested, while both species show a declining performance with increases in memory load. This relationship is consistent with that observed in studies explicitly comparing human and monkey performances on other working memory tasks. For example, it has been shown that monkeys generally perform more poorly than humans on identical visual serial probe recognition tasks, but they exhibit similar primacy and recency effects (Roberts & Kraemer, 1981; Sands & Wright, 1980). This similarity in the psychophysical functions relating task performance to experimental manipulations of mnemonic processes across species has been attributed to common underlying memory mechanisms (Sands & Wright, 1980). The similar memory load effect on change detection performance observed in both humans and monkeys likewise suggests common neural substrates. On this basis, studying change detection in monkeys provides a valuable animal model for investigations of the neural mechanisms underlying working memory and its information processing limitation.

Several models of the limit of information processing inherent to visual working memory have been proposed to account for findings of psychophysical studies with human subjects. Generally speaking, such models fall within three classes: (1) "slot" models, which assert that capacity limits are a consequence of a limited number of discrete, fixed resolution slots available within working memory (Awh et al., 2007; Cowan, 2001; Luck & Vogel, 1997; Rouder et al., 2008; Zhang & Luck, 2008); (2) resource allocation models, suggesting that working memory represents the flexible allocation of a limited resource (Bays, Catalao, & Husain, 2009; Bays & Husain, 2008; Wilken & Ma, 2004); and (3) hybrid models, postulating a combination of processes (Alvarez & Cavanagh, 2004; Xu & Chun, 2006). These competing accounts are useful frameworks to guide the investigations of the neural basis of working memory and the interpretation of such data, but none of them have been validated at the neural level. Thus far, evidence from EEG and brain imaging studies in humans performing change detection tasks has been marshaled in support of both slot (Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004) and hybrid (Xu & Chun, 2006) models. Studies of neuronal activity in monkeys within a similar psychophysical context have the potential to fully address this enduring issue by elucidating the exact relationship between neural representations and working memory ability across its entire operating range.

An understanding of the neural mechanisms underlying the information processing limits of working memory could provide significant advances on three fronts. First, the limitations of visual working memory can serve as a proxy for those dictating allocation of cognitive resources in a general sense. It has been suggested, for example, that visual working memory shares a common limit with both reasoning ability (Halford, Cowan, & Andrews, 2007) and the ability to filter irrelevant information (Vogel et al., 2005). Second, the observation of impaired visual working memory in patients afflicted with psychiatric disorders such as schizophrenia (Gold et al., 2006) suggests that an understanding of the neural processes underlying limits of visual working memory will be of significant value in deconstructing the functional changes in neural circuitry underlying psychiatric illness. Indeed, a precedent for this approach has been established with respect to working memory in other tasks (Goldman-Rakic, 1999). Finally, investigation of the correlates of capacity limits at the neuronal level, in combination with psychophysical studies and measures of neural activity in humans, represents a synthetic approach to understanding the limits of information processing and neural basis of cognitive processes.

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