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VARIABILITY IN NEURONAL ACTIVITY IN PRIMATE CORTEX DURING WORKING MEMORY TASKS

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Abstract—Persistent elevated neuronal activity has been identified as the neuronal correlate of working memory. It is generally assumed in the literature and in computational and theoretical models of working memory that memory-cell activity is stable and replicable; however, this assumption may be an artifact of the averaging of data collected across trials, and needs experimental verification. In this study, we introduce a classification scheme to characterize the firing frequency trends of cells recorded from the cortex of monkeys during performance of working memory tasks. We examine the frequency statistics and variability of firing during baseline and memory periods. We also study the behavior of cells on individual trials and across trials, and explore the stability of cellular firing during the memory period. We find that cells from different firing-trend classes possess markedly different statistics. We also find that individual cells show substantial variability in their firing behavior across trials, and that firing frequency also varies markedly over the course of a single trial. Finally, the average frequency distribution is wider, the magnitude of the frequency increases from baseline to memory smaller, and the magnitude of frequency decreases larger than is generally assumed. These results may serve as a guide in the evaluation of current theories of the cortical mechanisms of working memory. © 2007 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: spike trains, monkeys, memory networks, parietal cortex, prefrontal cortex, computational models.

The electrophysiological study of the neuronal basis of working memory in primates has traditionally focused on the changes in single-cell average frequency that may occur during the mnemonic retention of a stimulus cue in delayed-response tasks. Experiments dealing with this issue have led to the identification of cells, generally labeled "memory cells," that show a persistent increase in their average firing frequency (AF) during the memory period of a memory task (Fuster, 1997). Memory cells have been identified in multiple cortical regions, including prefrontal (Fuster and Alexander, 1971; Fuster, 1973; Niki, 1974; Niki and Watanabe, 1976; Funahashi et al., 1989; Miller et al., 1996; Rao et al., 1997; Romo et al., 1999), parietal (Gnadt and Andersen, 1988; Koch and Fuster, 1989; Andersen et al., 1990; Barash et al., 1991; Zhou and Fuster, 1996, 1997), and inferotemporal (Fuster and Jervey, 1981, 1982; Miyashita and Chang, 1988; Fuster, 1990; Miller et al., 1993; Chelazzi et al., 1993, 1998; Colombo and Gross, 1994; Gibson and Maunsell, 1997) cortex. A variety of studies have shown that memory cells in all three of these associative regions are involved in the retention of a given sensory cue for a prospective motor response. It has also been shown that cells within a given region can retain associated items of more than one modality (Haenny et al., 1988; Maunsell et al., 1991; Colombo and Gross, 1994; Bodner et al., 1996; Gibson and Maunsell, 1997; Zhou and Fuster, 1997, 2000; Fuster et al., 2000). The bulk of this empirical evidence suggests that the retention of a sensory cue in working memory may involve the sustained activation of a widely distributed and dispersed cortical network. A related idea is that a single cell can be part of many different working memory networks, and thus participate in the mnemonic retention of different memoranda (Amit, 1995; Fuster, 1995). Alternatively, the presence of memory cells in multiple cortical regions may simply indicate that working memory is a redundant process, with independent working-memory function occurring in multiple cortical regions.

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Abbreviations: AF, average firing frequency; CM, cross-modal; CV, coefficient of variation; CVAF, coefficient of variation of the average firing frequency; $CVAF_{cm}$, coefficient of variation of the average firing frequency of cell c to memorandum m; CV-ISI, coefficient of variation of the interspike intervals; $CVISI_{cm}$, average coefficient of variation of the interspike intervals for cell c across all trials with memoranda m; DMS, delayed-match-to-sample; F_{cm}, memorandum-specific cell response, average firing frequency of cell c to memorandum m across all trials with m; F_{cm}^{delay}, delay-period memorandum-specific cell response, delay-period average firing frequency of cell c to memorandum m; F_{cmt}, average firing frequency of cell c to memorandum m on trial t; F_{cmt}^{base}, baseline-period average firing frequency of cell c with memorandum m on trial t; FF, Fano factor; FF_{cm}, average Fano factor for cell c across all trials with memoranda m; I_D, discriminability index; P_{CVAF}^{DA}, average coefficient of variation of the average firing frequency of all cells with a delay-activated response; P_{CVISI}^{SDA}, average coefficient of variation of the interspike intervals across all cells with a stable delay-activated response; P_m^{DA}, average memorandum-specific cell response of all cells with a delay-activated response to memorandum m; P_m^{delay}, delay-period firing frequency of all cells in response to memorandum m; P_{FF}^{SDA}, average Fano factor across all cells with a stable delay-activated response; SD, standard deviation; SDR, spatial delayed-response; VR, variance ratio.

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The cortical mechanisms by which a network stays in the active state during working memory, however, are as yet undetermined. Determining the principles by which the cortex retains information requires an understanding of (1) the underlying computational processes, (2) the patterns of activation that result from those processes, and (3) the relevance of those patterns to memory function. Based on some aspects of the neuroanatomy of the cortical regions involved in working memory, it has been postulated that the sustained activation seen in working memory is primarily a result of the reverberating circulation of impulses through reentrant circuits of local and global cortical networks (Hebb, 1949; Amit, 1989; Sporns et al., 1989; Tononi et al., 1992; Zipser et al., 1993; Amit, 1995; Amit and Brunel, 1997a,b; Brunel, 2000a; Laing and Chow, 2001; Gutkin et al., 2001). Alternatively, it has also been suggested that the sustained activation observed in some cells during working memory primarily results from intrinsic cellular bistability produced by long-lasting synaptic and/or cellular conductances (Marder et al., 1996; Delord et al., 1997, 2000; Lisman et al., 1998; Haj-Dahmane and Andrade, 1998; Wang, 1999; Fransen et al., 2002, 2006; Egorov et al., 2002; Durstewitz, 2003; Loewenstein and Sompolinsky, 2003), synaptic dynamics and/or dendritic bistability (Goldman et al., 2002, 2003; Kitano et al., 2002; Amit et al., 2003; Renart et al., 2003), neuromodulatory influences (Durstewitz et al., 2000; Seamans et al., 2001; Tanaka, 2002; Camperi and Manias, 2003), or a combination of the above (Camperi and Wang, 1998; Compte et al., 2000; Brunel and Wang, 2001; Tegnér et al., 2002; Koulakov et al., 2002; Miller et al., 2003; Mongillo et al., 2005; Chadderdon and Sporns, 2006; Compte, 2006). Models based on those factors have successfully produced persistent cue-selective increases in cellular firing frequency in discrete subpopulations of cells.

However, it has so far been difficult to directly assess the relative plausibility of these various models of cortical working memory. This may partly be because the published experimental data they generally attempt to replicate are often obtained by averaging across trials, thus obscuring within-trial and across-trial variability. Furthermore, for the purpose of concise presentation, individual papers often publish statistics for no more than a few "prototypical" cells, with the result that information regarding cell activity relative to the network population background is often obscured. However, such information may be particularly relevant in evaluating different models, as those models may have different requirements for memory activity, and/or make different predictions regarding tolerance to noise and variability (see for example Miller and Wang, 2006; Compte, 2006).

Recent experimental studies have extended the analysis of cellular behavior to examine the temporal trends in neuronal activity during the delay period of working memory tasks (Miller et al., 1996; Quintana and Fuster, 1999; Romo et al., 1999, 2002; Erickson and Desimone, 1999; Pesaran et al., 2002; Rainer and Miller, 2002; Brody et al., 2003a,b; Compte et al., 2003; Romo and Salinas, 2003; Durstewitz and Seamans, 2006). Some of those studies have highlighted firing trends that vary over time in the delay period, while others have indicated that cells apparently encoding the memorandum during the memory period may also be involved in the preparation of the upcoming motor response. Recently, models to explain these alternate behaviors have been developed (Durstewitz, 2003; Mongillo et al., 2003; Reutimann et al., 2004; Durstewitz and Seamans, 2006).

In the light of the evidence summarized above, it appears that the understanding of the functional mechanisms of working memory requires further evaluation of neuronal behavior in memory tasks. The present study attempts to provide a quantitative survey of the temporal variance in the firing frequency behaviors of cells in different cortical areas during working memory tasks. The database consists of extracellular unit records from areas implicated in working memory of the specific modalities of the memoranda used by the animal in the respective tasks, and thus represents typical cell activity during working memory. Specifically, the database of our study consists of 521 parietal cells recorded from one monkey during a haptic delayed-match-to-sample task (Zhou and Fuster, 1996), 291 cells recorded from prefrontal cortex of a different monkey during a cross-modal (CM) audiovisual delayed-matching task (Bodner et al., 1996; Fuster et al., 2000), and 149 cells recorded from prefrontal cortex of a third monkey during alternating visual delayed-match-to-sample (DMS) and spatial delayed-response (SDR) tasks (Quintana et al., 1988). Various statistical parameters of the three populations of cells are assessed. Cells are categorized on the basis of the trends of their average-across trials-firing in memory periods, and the average frequency statistics for each of the identified categories is examined. The frequency behavior of cells on individual trials is then analyzed, and the results of this analysis compared with both the average-across trials-frequency statistics and with predictions from theoretical models. Finally, the stability of cellular firing over the course of any given trial is evaluated.

EXPERIMENTAL PROCEDURES

Single unit recording

The database for this study consists of 961 cells. In that sample, there are 521 parietal cells recorded from areas 2, 3, 5, and 7 of one monkey during performance of a haptic delayed-matching task (Zhou and Fuster, 1996); 291 prefrontal cells recorded from areas 6, 8, 9 and 46 of another monkey during performance of a CM audiovisual task (Bodner et al., 1996; Fuster et al., 2000); and 149 prefrontal cells recorded primarily from area 9 and the dorsal portion of area 46 of a third monkey during performance of alternating visual (DMS) and SDR tasks (Quintana et al., 1988). Thus, all parietal and prefrontal cells were recorded during delayed-response tasks. In these tasks, the monkey was presented with a cue stimulus which had to be retained in memory through the delay period. At the end of the delay period, the monkey was required to choose between different stimuli, with the correct choice contingent on the cue. Thus, the common element to all tasks was the necessity to retain information about the cue in working memory.

The parietal cells were recorded from the hemisphere contralateral to the hand with which the monkey performed the haptic task. A trial in this task consisted of the following events: (1)