

A Code for Cross-Modal Working Memory

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In this issue of *Neuron*, Vergara et al. (2016) report that neurons in the pre-supplementary motor area represent the frequency of tactile and auditory stimuli held in working memory. Single neurons encode both types of information by using the same representation for both modalities.

We live in a multisensory world that bombards our sensory receptors with stimuli of all kinds. Our brains have evolved the ability to combine the input of different senses (Stein and Stanford, 2008), but also to transform effortlessly information between sensory modalities. We hear a new acquaintance tell us her phone number and we are able to find the corresponding digits on a cell-phone screen. Those with musical training can read a page of music and recall the melody, without ever hearing it on an instrument. In blindfold games, children can explore a toy by touch and then answer questions about it. In all of these examples, information in one sense was perceived, stored in working memory, and then compared to information from another sense. Where in the brain does this comparison happen, and what is the nature of the cross-modal code?

Human studies have revealed several instances of cortical areas that can represent information about stimulus features, generalizing across multiple modalities. Visual cortex is activated during tactile discrimination of orientation (Zangaladze et al., 1999). Braille reading similarly activates areas involved in visual shape discrimination (Sadato et al., 1998). Even more abstract information encoding, not tied to any specific modality per se (amodal processing), has been identified in the human prefrontal cortex (Tamber-Rose-nau et al., 2013). Yet the neural correlates of cross-modal working memory comparisons have remained elusive. In fact, where and how working memory information of any sensory modality is stored has been a matter of debate in recent years (D'Esposito and Postle, 2015; Riley and Constantinidis, 2015). Traditional views considered working memory to be mediated by the persistent activity of neurons

of the frontal lobe, most importantly in the lateral prefrontal cortex. This idea has been questioned, mostly as a result of human fMRI studies that have been successful in decoding working memory information from the primary visual but not the prefrontal cortex (Harrison and Tong, 2009). It has been an open question, therefore, how single neurons can represent information about a stimulus quality across different modalities, and where these reside in the brain.

In this issue of *Neuron*, Vergara et al. (2016) address this question by examining how the frequency of tactile and acoustic stimuli is maintained in working memory. The authors trained monkeys to perform a cross-modal, frequency comparison task. In some trials, a tactile flutter stimulus was presented, vibrating at a frequency between 8 and 32 Hz. The monkey was required to remember the frequency of the vibration over a delay period lasting a few seconds. Then a second stimulus was delivered, and the monkey had to decide if its frequency was lower or higher than the first. In a twist of this basic task, which has been very successfully used to explore responses to tactile stimuli in large swaths of the cerebral cortex (Romo et al., 2012), either the first or the second stimulus could be auditory. The auditory stimulus comprised a series of tones separated by intervals of silence. By varying the duration of the intervals, the frequency of the tone pulses could also vary between 8 and 32 Hz. The monkey's task then became to compare the two frequencies and decide if the second was higher than the first, with no regard to the sensory modality of the stimuli (Figure 1). Although the task appears simple, training monkeys to perform it was quite an achievement in itself. Macaque monkeys, by all ac-

counts highly intelligent animals, are notorious for their determined indifference to auditory stimuli in laboratory tests of working memory.

Potential candidate areas that could represent frequency in working memory included the lateral prefrontal cortex, which is known to be active during working memory in cross-modal tasks (Fuster et al., 2000), and the primary sensory cortex of the auditory (A1) and somatosensory system (S1), if working memory is in fact stored in sensory cortex. Recent work by the authors, however, had explicitly ruled out that the cross-modal code for an auditory-tactile comparison could have resided in S1 or A1. Neurons in each area encode only their individual modalities and only during the stimulus presentation period (Lemus et al., 2010). The authors chose instead an area in the medial surface of the frontal lobe, the pre-supplementary motor area (pre-SMA). This was a strategic choice, driven partly by an existing body of knowledge about the responses of pre-SMA neurons to tactile stimuli during the frequency comparison task and its activation during working memory (Hernández et al., 2002, 2010). At the same time, the study provided the opportunity to test if information about cross-modal stimulus features is represented in frontal cortex, in a working memory task.

As was expected, when the monkeys were remembering the frequency of an initial tactile stimulus in order to perform the comparison with the upcoming second stimulus, pre-SMA neurons were active during the delay period. Neurons were also found to be active when the monkey heard the acoustic stimulus first. Importantly, the same neurons exhibited nearly identical patterns of responses to the two types of stimuli during working

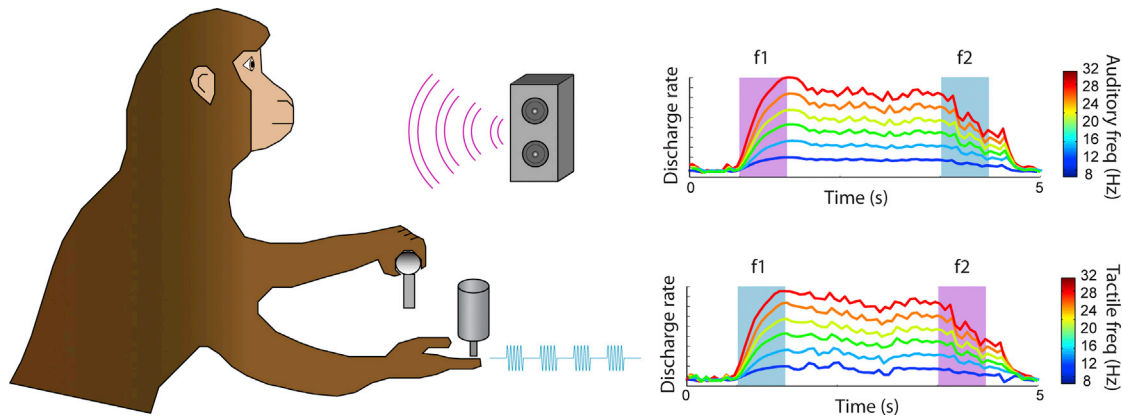


Figure 1. A Cross-Modal Code for Working Memory

Left panels illustrate the behavioral task (Vergara et al., 2016). The monkey is required to compare the frequency of two stimuli presented in sequence, with a delay period between them. The stimuli may be tactile or auditory, requiring the monkey to make a cross-modal comparison. Right panels represent schematically the responses of a single neuron in the pre-supplementary motor area. Discharge rate is shown (top) when an auditory stimulus was presented first (purple bar) followed by a tactile stimulus (blue bar), or vice versa (bottom). Responses of the neuron during the delay period were modulated monotonically depending on the frequency of the stimulus, adhering to the same monotonic code of firing rate as a function of frequency for both the remembered auditory and tactile stimuli.

memory (Figure 1). Individual neurons exhibited delay-period firing rate that was rising as a function of increasing frequency of the tactile and auditory stimulus (Figure 1), or delay-period firing rate that was decreasing for higher frequencies of both stimuli. The results establish pre-SMA as an area participating in cross-modal working memory, but more importantly uncover a common code for remembered frequency, regardless of the modality in which this was transmitted. The findings reveal how individual neurons can perform an abstract cognitive function based on inputs from different sensory modalities.

The results also inform the debate about the site of working memory information in the brain. As mentioned above, recent studies have postulated that sensory cortices mediate the representation of features of sensory stimuli in working memory, whereas frontal areas contain no content information in working memory but merely serve to provide a top-down signal (D'Esposito and Postle, 2015). The results in the pre-SMA, a medial frontal area with no direct sensory input, argue directly against this model. The frequency of auditory and tactile stimuli was encoded precisely in the firing pattern of the pre-SMA neurons, rather than a general, top-down signal representing the location of the stimulus in space, or the feature of the stimulus that needed to be remembered. The study

adds to a number of recent studies finding correlates of stimulus features in the frontal cortex during working memory, such as the orientation of a visual grating or the direction of motion of dots in a fixed aperture (Ester et al., 2015; Mendoza-Halliday et al., 2014).

As is often the case with an intriguing experimental result, the study opens up as many new questions as it answers. One line of questions has to do with which other cortical areas exhibit working memory with a common code for different modality of stimuli and where this supramodal code appears first. The lateral prefrontal cortex, which provides anatomical input to pre-SMA, represents a likely area, though not necessarily the first node where such a code emerges in the cortical network. A recent study obtaining recordings from multiple cortical areas has revealed abrupt emergence of delay-period activity for direction of motion in area MST, preceding the appearance of delay-period cortex in the prefrontal cortex (Mendoza-Halliday et al., 2014). A similar approach across the auditory and somatosensory pathways could help answer this question for cross-modal working memory. A second line of questions has to do with the comparison of the cross-modal code. How do neurons in the auditory-tactile frequency task respond to a second stimulus when it is of higher or lower frequency than the preceding one but belongs to a different

modality? Neurons exhibiting decision variables have been described in the pre-SMA (tested exclusively with tactile stimuli, so far), for example displaying a categorical preference for a second stimulus of higher rather than lower frequency (Hernández et al., 2010). The dataset obtained by Vergara et al., (2016) will likely reveal how neural correlates of decision variables in neural activity are also modulated independent of modality. Finally, what are the neural codes of other types of information represented in working memory regardless of modality, or even amodal processing? The richness of the natural world that allows us to do cross-modal comparisons is often lost in laboratory experiments relying on a reductionist approach to study neural correlates of elemental cognitive operations, by using as simplified and controlled conditions as possible. The experimental design devised by the authors provides a model that can be emulated to address complex representation of other types of information, as well.

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Pondering the Pulvinar

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While the function of the pulvinar remains one of the least explored among the thalamic nuclei despite occupying the most thalamic volume in primates, it has long been suspected to play a crucial role in attentive stimulus processing. In this issue of *Neuron*, Zhou et al. (2016) use simultaneous pulvinar-visual cortex recordings and pulvinar inactivation to provide evidence that the pulvinar is essential for intact stimulus processing, maintenance of neuronal oscillatory dynamics, and mediating the effects of attention.

It is customary to think of the thalamus as the switching station of the brain, through which cables carrying information from the outside world are switched over to cortex-bound cables where the information is then deciphered. In recent years, this simple view has undergone significant changes, driven in part by anatomical studies showing that thalamic relay nuclei consist of two types of thalamo-cortical projection systems: topographically organized, specific projections originating in the “core” regions of thalamic nuclei, and more diffusely projecting nonspecific projections originating in the thalamic “matrix” (Jones, 1998). While specific inputs carry detailed sensory information and project to the granular layer—the classical input layer—of primary sensory cortices, nonspecific modulatory projections predominantly target the supragranular layers of a wider array of cortical areas and are thought to be responsible for aligning internal excitability patterns to the timing of relevant sensory inputs, providing the neuronal context in which the hierarchically trans-

mitted content, or specific information, is processed (Lakatos et al., 2013). Another important anatomical finding instigating the changing view of the thalamus is that a number of thalamic nuclei receive a dominant part of their input not through pathways ascending from sensory organs, but from the cortex, for routing to other cortical or subcortical structures (Guillery and Sherman, 2002).

The largest of these nuclei is the pulvinar, which occupies approximately a third of thalamic volume in humans and most non-human primates but is relatively miniscule in rodents (Chalfin et al., 2007). One could therefore argue that the pulvinar is likely to be involved in brain operations that are more elaborate in higher-order mammals. However, while the anatomy of the primate pulvinar is reasonably well described (Arcaro et al., 2015), there is very little information about its function. Nonetheless, previous research indicates that the pulvinar is indeed involved in high-level functions like attention, social cognition, and speech processing. Thus, unsurprisingly, impaired pulvinar function

is implicated in numerous psychiatric disorders including schizophrenia and ADHD (Benarroch, 2015). The clinical relevance and functionally significant role of the pulvinar in cognitive processes highlights the crucial role that non-human primate studies can play in enabling the mechanistic analysis of the multi-faceted pulvinar function.

The study by Zhou et al. (2016) published in this issue of *Neuron* takes a significant step in the direction of determining the role of the pulvinar in attentive stimulus processing. First, in order to directly compare response properties and test for interactions in sites with overlapping receptive fields, the authors simultaneously recorded neuronal activity in ventro-lateral pulvinar and visual cortex (V4 and IT) in awake monkeys. A comparison of response properties showed that pulvinar receptive field size and stimulus selectivity is intermediate between V4 and IT cortex, consistent with its proposed role of transmitting visual information from lower- to higher-level nodes of the visual information processing