Neural coding of attention and attentional set shifting in the rat medial prefrontal cortex

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Chapter 5

When previously irrelevant information becomes relevant:
temporal rearrangement of ensemble firing patterns
in the rat medial prefrontal cortex
in an attentional set shifting task

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About the illustration: 3D maps of ensemble activity during the head retraction period following a positive stimulus (cf. Fig.5-2A)
Temporal rearrangement of ensemble firing patterns in the rat mPFC

Abstract

Attentional control in the temporal domain is considered a cardinal function of the prefrontal cortex, and this function becomes especially relevant when the relevance of sensory input changes. Here we studied how ensemble firing patterns in the medial prefrontal cortex are altered when rats perform a multimodal attentional set shifting task. When the rat successfully performed the task, neural representations showed a temporal rearrangement of ensemble firing patterns during extradimensional shifting as compared to simple discrimination. The rearrangement of firing activity related to decision-making and motor preparation was stronger than when intradimensional shifting or compound discrimination phases of the task were compared. However, when the animal failed to shift its attentional set, the ensemble patterns showed a high preservation during extradimensional set shifting. These results suggest that an attentional switch from one sensory modality to another is accompanied by a dynamic regrouping of prefrontal network activity.

When one studies in a library, one needs to focus on reading a book while ignoring noise from the surroundings. However if someone calls you, you need to shift your attention away from the book and towards this person. In cognitive control, active maintenance of relevant information against a background is crucial, as is the ability to shift attention when previously relevant inputs are no longer associated with a goal of interest (Miller and Cohen, 2001). The prefrontal cortex (PFC) has been strongly implicated in attentional control (Nagahama et al., 2001; Hampshire and Owen, 2006; Rossi et al., 2009), as exemplified by its dysfunctioning in disorders such as schizophrenia, attention deficit hyperactivity disorder (ADHD), and Parkinsonism (Downes et al., 1989; Elliott et al., 1995; Arnsten, 2009). Schizophrenic patients suffer, amongst others, from a high distractibility under conditions of attentional conflict (Chao and Knight, 1995; Rogers et al., 1998; Jazbec et al., 2007) and difficulties in shifting attention when previously irrelevant information becomes relevant (Goldberg et al., 1987; Owen et al., 1993).

Attentional set can be defined as a dispositional, experience-dependent state of attentional ‘readiness’ of an animal to focus reliably and efficiently on elements of a task or cognitive problem (Buchwald et al., 1975; Dias et al., 1996b). Based on Mackintosh’s theory of selective attention in discrimination learning, attentional set shifting is hypothesized to involve several components, viz. (i) inhibiting an old set, (ii) attending to a previously ignored stimulus dimension (reallocation of attention), (iii) forming new stimulus-response associations, and (iv) forming new stimulus-outcome associations (Mackintosh, 1965; Mackintosh, 1975). The dorsolateral PFC in primates and the medial prefrontal cortex (mPFC) in rats have been shown to be specifically involved in attentional set shifting, especially in components (i) and (ii). In contrast, the orbitofrontal cortex has been implicated in reversal learning, in which reward contingencies are switched from one stimulus to another, involving component (iv).
(Dias et al., 1996b; Birrell and Brown, 2000; O’Doherty et al., 2001; Schoenbaum et al., 2002). Recent findings have indicated the anterior cingulate cortex is involved in component (iii) (Kondo et al., 2004; Johnston et al., 2007; Ragozzino and Rozman, 2007; Lapish et al., 2008).

Figure 5-1. **Behavioral cage, exemplars and task sequence.** A. Behavioral cage with the multimodal stimulus (MMS) chamber and a fluid well. For illustrative purposes, the front wall of the MMS chamber is drawn as if transparent. The behavioral cage included (a) a light for signalling trial onset, (b) a head-entry port for gaining access to the MMS chamber, (c) a horizontal shelf upon which the rat put its forepaws during stimulus sampling, and (h) a well for delivering fluids. Inside the MMS chamber, (d) an odor delivery nozzle was placed at the bottom, (e) the LCD screen with (f) a visual pattern was located at the rear side, and (g) a camera for viewing head entry behavior was fixed at the
Because attentional control is likely to be determined by large, coordinated groups of neurons, neurophysiological mechanisms of attentional set shifting need to be analyzed at the population level. Ensemble recordings provide the opportunity to measure population firing patterns in the brain of behaving animals (Wilson and McNaughton, 1993). Previous ensemble recording studies have provided insights in population coding of spatial location (Wilson and McNaughton, 1993; Zhang et al., 1998), reward expectation (van Duuren et al., 2008) and working memory (Baeg et al., 2003), but it is unknown how the principles uncovered for these processes may be translated to coding of attentional set and task rules. Here we chose to analyze attentional control by studying shifting across sensory modalities, first because it is practically feasible to apply multimodal stimuli to rodents and second because cross-modal attention reflects a highly integrated type of control that likely depends on the
mPFC and connected regions where convergence of multisensory inputs takes place (Fuster et al., 2000; Miller and Cohen, 2001). An important component of studying executive attention in rodents (Mackintosh, 1975; Posner and Dehaene, 1994; Robbins, 1996) is the problem of dissociating attention from changes in motor behavior as an animal is subjected to different attentional conditions (cf. Euston and McNaughton, 2006). Although it may be questioned whether a strict segregation between attention and motor behavior truly exists in rodents, we aimed to train animals on a protocol that maximizes stereotyped, regular behavior as well as body posture during sensory processing, when attention needs to be (re)directed to make correct decisions. Given demonstrable regularity (cf. chapter 2), neural coding of attentional shifts may thus be accessible for study. Thus we designed a multimodal discrimination task set in a chamber where visual and odor stimuli could be simultaneously presented to a rat in a time-controlled manner (Fig.5-1A) and investigated ensemble coding of task events in mPFC of freely moving rats using multi-tetrode recording techniques.

The learning task required the rat to insert its head into the chamber for 1 s, during which one or two stimuli could be simultaneously presented (e.g. grass odor and a visual pattern). All sessions started with a simple discrimination protocol requiring a Go/NoGo response to a pair of exemplars in one sensory dimension (olfaction). Fig.5-1B shows a trial sequence in the task from trial onset to reinforcement consumption. Exemplars used in the experiments are shown in Fig.5-1C. After simple discrimination (SD) the rat was subjected to the next task stages, viz. compound discrimination (CD; in which a stimulus from an irrelevant dimension was co-presented with a relevant, outcome-predicting stimulus), intra-dimensional shifting (IDS, where new stimuli were applied in both dimensions but the relevance or irrelevance of each dimension was maintained) and extra-dimensional shifting (EDS, where new stimuli were applied in both dimensions and the relevant dimension became irrelevant whereas the previously irrelevant dimension became relevant; for a more complete overview, see chapter 4; in some sessions, the IDS phase was omitted). Transitions between task stages were contingent on the rat’s performance meeting a particular criterion (generally: 70% correct rejections in response to S- trials in a block containing 8 S+ and 8 S- trials, however one session with 60% correct rejection in IDS was added to the analysis). Whenever the rat performed 10 consecutive trials without omissions after the EDS phase, a control stage using visual discrimination of familiar stimuli was run.

We analyzed a total of 206 single-units from 6 sessions (2 rats), of which 136 units showed behavioral correlates to one or more trial events in the attentional set shifting task. In 5 sessions (from one rat), the full sequence of SD-CD-IDS-EDS could be run, whereas we also used one other session (from the other rat) in which a SD-CD-EDS sequence was run. To compare neural ensemble representations across different task
stages, we used a similarity index that was described in chapter 3 and was derived from earlier template matching methods (Louie and Wilson, 2001; Tatsuno et al., 2006). This measure of the consistency of ensemble representations incorporates a normalization based on within-SD similarity. We divided the data into two sets of sessions which showed a high and low performance accuracy in the EDS phase. The accuracy was defined as the sum of the number of Hits (i.e. correct responses in S+ trials) and the number of Correct Rejections (NoGo responses in S- trials), divided by the total number of trials.

Figure 5-2. Firing patterns and similarity index of all task-correlated mPFC neurons (n=80) during high-accuracy performance of the multimodal attentional set shifting task. Sessions (N=3) were included if rats succeeded in performing the EDS switch within the same session and if the session took place before or after this session. (A) Ensemble map for correct S+ (Hit) trials during simple and compound discrimination, intra- and
Accuracy in the well-performed EDS sessions (N=3 from one rat) was 72.7 ± 5.1 % and accuracy in the poorly performed sessions (N=3 from two rats) was 50.8 ± 1.8 %, respectively. In the CD phase, neural representations were highly similar to those in SD, especially on Hit trials and significantly less so on Correct Rejection trials (Wilcoxon test, p<0.05; Fig.5-2). The number of False-Alarm responses was too low to allow meaningful comparisons. When the IDS and EDS phases were compared for the high-accuracy sessions, the strongest change relative to SD occurred when the relevant and irrelevant dimension were switched (EDS) and not just upon presentation of new stimuli (IDS; Fig.5-2, Wilcoxon test, indicated by asterisk) for both Hits and Correct Rejections, but not for the stimulus sampling period. (B) Idem as (A) but for Correct Rejection trials. Here the rat refrained from going to the fluid well.
In Fig. 5-4, we illustrate another type of analysis applied to our mPFC neural data set: first we used a k-means algorithm to partition the ensembles recorded in 3 high-accuracy sessions in four clusters of neurons, based on their temporal, task-related firing profiles in the SD phase. Next, we studied changes in these four temporal profiles across later task stages (CD, IDS and EDS) and quantified whether they differed significantly from the SD profile. During EDS, average cluster responses showed significant decrements or increments in amplitude during the stimulus sampling and head retraction periods, indicating that dynamic changes occurred especially during stimulus processing, decision-making and preparation for action (indicated by asterisks (*) for decrements and # for increments (Kolmogorov-Smirnov (KS) test, p<0.001). Moreover, at least one cluster profile started earlier around head retraction time in EDS as compared to SD, CD and IDS (indicated by...
in Fig.5-4A and Fig.5-4D, KS test, p<0.001). These results indicate that changes in dimensional relevance, as in EDS, correlate with a temporal repatterning of mPFC ensemble activity. This EDS repatterning is stronger than seen during IDS, which also involves formation of new stimulus-outcome and stimulus-action associations, but critically lacks the switch in dimensional relevance.

Figure 5-4. Neural activity in each trial period was clustered for sessions with high-accuracy performance. Each panel, consisting of four colored curves (e.g. for the sucrose delivery trial period in the CD phase), displays the temporal profile of firing activity for each of the 4 clusters. These clusters were identified in the SD phase. The number of clusters in the K-means algorithm was set to 4, which resulted in SW values ranging around 0.5 in the SD phase. We maintained the same clusters in each phase to compare changes of clustered activity across different phases. Neural data were the same as in Fig.5-2A. (A) Z-scores of clustered firing rates are represented both by the color of the curve and by its excursion in the direction of the ordinate. Z-scores were truncated to the range [-5 5] for illustrative purposes, thus scores
At a neural level, attention has been proposed to be expressed by an enhanced activity in response to relevant stimuli and a suppression of responses to irrelevant inputs (Pashler, 1998; Posner, 2004). Our data are consistent with the hypothesis that changes in sensory input and individual stimulus-outcome contingencies can be internally represented as amplitude increments or decrements of individual neural firing responses (i.e., rate modulation), as long as an attentional set is maintained. However, when a previously relevant dimension becomes irrelevant and attention is required to shift to a previously irrelevant dimension, priorities in information handling need to be changed as well. We propose that this process is mediated by a dynamic reorganization of mPFC activity, which we suggest here is not only expressed by individual neurons (chapter 4) but also by global measures of ensemble activity (Fig.5-2,3,4). We raise this suggestion with caution because of the low number of available sessions. Despite this limitation, it is important that our ensemble measures indicated a repatterning of mPFC activity, because changes at the level of individual neurons may be argued to be incidental and due to random fluctuations. As Fuster has pointed out (Fuster et al., 2000), the cardinal function of PFC is to exert cognitive control in the temporal domain. As a specific instance of cognitive control, reallocation of attention at the correct time and in task-appropriate brain areas is crucial for an animal’s navigation through the web of task rules and contingencies.

SUPPLEMENTARY DATA: CLUSTER ANALYSIS

Smoothed peri-stimulus time histograms (PETHs) of single units were transformed into Z-scores, based on the mean firing rate of a single unit across a window of 1.0 sec (placed around the task event of interest: -0.3 to +0.7 s, -0.5 to +0.5 s, -0.5 to +0.5s, respectively; Fig.5-2,3,4), which was subtracted from each bin value during the SD...
phase and corrected for variance, in order to compare ensemble activity patterns across task phases, viz, SD, CD, IDS, EDS and the SD control phase. To gain insight into how mPFC neurons are clustered based on their task-related temporal profiles, we first composed a matrix $X$ containing Z-scored firing rates of different neurons across $n$ bins, viz., each matrix element $x_{in}$ represented the firing rate of cell $i$ at time bin $n$, and then applied the k-means algorithm (Martinez and Martinez, 2008, cf. Paz et al., 2005) to partition the Z-scores into $k$ clusters of neurons based on their temporal profiles. The k-means algorithm uses an iterative procedure to minimize an error which is defined as the total of within-cluster sums of squares:

$$
error \ E = \sum_{j=1}^{k} \sum_{i \in C_j} \sqrt{\sum_{m=1}^{50} (x_{im} - \bar{x}_{jm})^2},
$$

where $x_{im}$ is a vector of Z-scored firing rates of the $i^{th}$ neuron in cluster $C_j$, $\bar{x}_{jm}$ is the center of cluster $C_j$, which represents the averaged vector of the firing rates of all neurons which belong to that cluster, in the $m^{th}$ iteration. The total number of clusters is preselected and represented by $k$; individual clusters are indexed by $j$. To minimize convergence to local minima, each k-means procedure was repeated 50 times and each time a different set of centers was generated randomly. Across these 50 iterations the partitioning with the lowest error was selected. An example of a cluster is shown in Fig.5-S1. The number of clusters was validated by applying a “silhouette analysis” (Martinez and Martinez, 2008, cf., Paz et al., 2005). The silhouette width (SW) for the $i$-th neuron (a vector of firing rates) and the average SW ($SW_{upperscore}$) are defined by:

$$
SW = \frac{\sum_{i=1}^{N} SW(i)}{N} = \frac{\sum_{i=1}^{N} \frac{b_i - a_i}{\max(a_i, b_i)}}{N},
$$

where $a_i$ is the average distance between neuron $i$ and all other neurons in the same cluster and $b_i$ is the minimal average distance between neuron $i$ and all neighboring clusters which neuron $i$ does not belong to. Thus SW measures the distance between each point to other points in its own cluster compared with to points in other clusters. SW ranges from -1 to 1, and a value of 1 means that clusters are maximally distinct from each other, whereas -1 means a minimal degree of clustering.
Figure 5-S1. **Example of a cluster of multi-neuron firing activity during the stimulus sampling period, data from Fig.5-2.** The Z scored firing activity of each neuron participating in the cluster is drawn as a gray line and the group (cluster) mean is shown as a black line.

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