Stable numerosity representations irrespective of magnitude context in macaque prefrontal cortex

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Content

Zusammenfassung

Kognitiv anspruchsvolle Aufgaben erfordern, dass vielfältige verhaltensrelevante Information kodiert und verarbeitet wird. Dies geschieht im präfrontalen Kortex. In Aufgaben mit abstrakten, erlernten Kategorien, formen die kontextspezifischen Parameter das Antwortverhalten von PFC Neuronen. In dieser Doktorarbeit wurde untersucht ob und wie die Selektivität von PFC Neuronen für die „natürliche“ Kategorie „Menge“ durch den Einfluss des Kontexts verändert wird.

Zwei Makaken wurden darauf trainiert visuelle Mengen (unterschiedliche Anzahlen an Punkten) in einer Delayed-Match-To-Sample Aufgabe (DMS) zu unterscheiden. Während sie die Aufgabe lösten, wurden Einzelzellableitungen im rechten, lateralen präfrontalen Kortex durchgeführt. Während jeder Ableitsitzung wurde die Mengen-Aufgabe entweder alleine oder zufällig durchmischt mit Farben oder Linienlängen Aufgaben präsentiert.

Der Kontext der Mengenunterscheidung hatte keinen Effekt auf das Antwortverhalten von „Zahlenzellen“. Die Abstimmkurven der mengenselektiven Zellen waren bleiben stabil undabhängig davon ob die Mengen im reinen oder im gemischten Block präsentiert wurden. Diese Daten legen nahe, dass Zahlenzellen des PFC ihre Antworteigenschaften nicht dem wechselnden Mengenkontext anpassen. Vielmehr scheint die Repräsentation von Mengen auf einem sparsamen, stabilen „labelled line“ Kode zu beruhen. Im Gegensatz zu erlernten Kategorien stellen Mengen eine “natürliche” Kategorie dar und könnten deswegen einen privilegierten Verarbeitungsweg im Gehirn einnehmen, der nicht zugunsten Verarbeitung anderer Inhalte adaptiert wird.

Abstract

Cognitively demanding tasks require neurons of the prefrontal cortex (PFC) to encode divergent behaviourally-relevant information. In discrimination tasks with arbitrary and learned categories, context-specific parameters shape and adapt the tuning functions of PFC neurons. We explored if and how selectivity of PFC neurons to visual numerosities, a “natural” abstract category, may change depending on the magnitude context. Two monkeys discriminated visual numerosities (varying numbers of dot items) in a delayed match-to-sample task while single cell activity was recorded from the lateral PFC. During a recording session, the numerosity task was either presented in isolation or randomly intermixed with delayed match to sample tasks with line lengths and colours as discriminative stimuli. We found that the context for numerosity discriminations did not influence the response properties of numerosity detectors. The numerosity tuning curves of selective neurons, i.e. the preferred numerosity and the sharpness of tuning, remained stable, irrespective of whether the numerosity task was presented in a pure numerosity block or a mixed magnitude block. Our data suggest that numerosity detectors in the PFC do not adapt their response properties to code stimuli according to changing magnitude context, but rely on a sparse and stable “labelled line” code. In contrast to arbitrarily learned categories, numerosity as a “natural” category may possess a privileged position and their neuronal representations could thus remain unaffected by magnitude context.

1 Introduction

The human brain has developed a variety of different specializations which allow us the uniquely human cognitive abilities such as language or higher mathematics. Humans have an especially enlarged frontal lobe within the cortex (Fuster, 2001; Petrides and Pandya, 1999). The frontal lobe contains the motor and premotor regions and lies directly anterior to the central sulcus and the prefrontal regions at the anterior pole of the brain (Zigmond *et al.*, 1999).

In this thesis I will first outline the importance of these prefrontal regions in primate evolution and their crucial role in cognition. I will describe the different models of cognition and prefrontal functions. The main concern of this thesis is the representation of magnitudes in the prefrontal cortex in non-human primates and the special role numerosities play in the primate cognition.

1.1 Prefrontal cortex

The evolutionary lines of humans and old world monkeys, which are frequently used in neurobiological research, diverged about 25 Mio years ago. Despite the long separation, and the fact that the human brain is 4.8 times larger than that expected for a monkey of comparable size (Passingham, 2009), both species share a lot of neuro-anatomical structures. The prefrontal cortex is the most recently evolved portion of the mammalian brain (Hendelman, 2000) and its dorso-lateral part is considered one of the true primate traits, not shared by other mammalian orders (Wise, 2008). It endows primates with the unprecedented cognitive abilities, they are able to display (Preuss, 1995).

1.1.1 Anatomy

The prefrontal cortex lies at the apex of the frontal lobe, anterior to the premotor areas (Hendelman, 2000). The different subdivisions of the frontal lobe are illustrated in Figure 1. The Brodmann areas 6, 24, 32 and parts of area 14 lack an internal granular layer IV and, hence, constitute the agranular cortex. These frontal areas are shared by primates and non-primate mammals. More anterior are the areas 8 and 14 that show a dysgranular cyto-architecture. At the rostral pole of the brain, anterior to the arcuate sulcus, lies the homotypical prefrontal cortex. This region exhibits a conspicuous granular input layer IV and, thus, is often termed the granular prefrontal cortex (Wise, 2008).

Different sources name different Brodmann areas as components of the PFC. In humans the medial section consists of the Brodmann areas 9-11 (Afifi and Bergman, 1998); the ventral section consists of the areas 12-14 and the dorsal section of 45-47 (Badre and D'Esposito, 2009; Miller and Cohen, 2001; Petrides and Pandya, 1999; Wise, 2008). Sometimes, the areas 8, 24, 32 and 44 are also considered to be a part of the prefrontal cortex (Fuster, 2001).

In monkeys, the prefrontal cortex can be classified into three major parts: the lateral, the medial and the orbitofrontal prefrontal cortex. Those subregions differ in their cytoarchitecture as well as in the connectivity patterns (summarized in Tanji and Hoshi, 2008). The granular dorso-lateral prefrontal cortex, the main object of this thesis, is the part of the brain which is only found in primates and the part that predominantly expanded through the primate evolution. About 30 % of the human neocortex is composed of the above prefrontal regions. By contrast, in old-world monkeys, such as rhesus macaques, the PFC only makes up about 11 % of the neocortical tissue (Passingham, 2009).

The granular PFC is a highly interconnected area. There are extensive connections within the frontal lobe itself (Barbas and Pandya, 1989; Kritzer and Goldman-Rakic, 1995), but in addition to those, the PFC receives a rich variety of inputs from all cortical

lobes. Higher sensory areas, including visual (Ungerleider *et al.*, 1989), somatosensory (Preuss and Goldman-Rakic, 1989), auditory regions (Petrides and Pandya, 1988) send highly processed information into the prefrontal cortex, resulting in multimodal neurons in the PFC (Watanabe, 1992). Furthermore, resting state fMRI studies reveal that the prefrontal cortex and the parietal association cortex have a strong functional connectivity pattern and thus form a fronto-parietal network (Damoiseaux *et al.*, 2006; Hutchison *et al.*, 2011; Vincent, *et al.*, 2008)

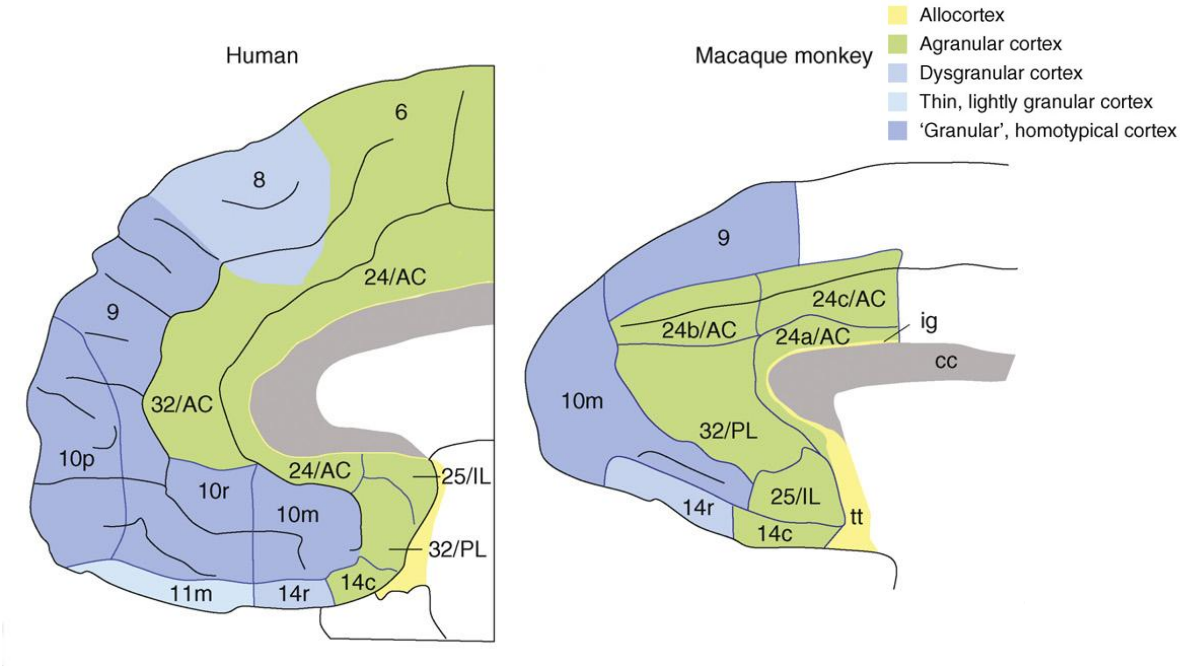

Figure 1: Mid-sagittal view of the frontal lobe of the human (a) and the rhesus monkey (b) brain. Granular prefrontal cortex (in blue) dominates the frontal lobe. Numbers refer to Brodmann areas (lower case letters indicated subdivisions within the area). AC: anterior cingulate area, PL: prelimbic cortex, IL: infralimbic cortex, cc: corpus callosum. Adapted from (Wise, 2008)

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Besides the neocortex, the PFC is also reciprocally connected to the limbic system, the basal ganglia and the thalamus (Barbas, 1995; Fuster, 2001). Historically, projections from the dorso-medial thalamic nucleus (MD) have been considered the characteristic of

the prefrontal cortex (Preuss, 1995). The MD nucleus is already highly integrative. It receives inputs from the amygdala, parts of the limbic system and the basal ganglia as well as hypothalamus and other thalamic nuclei (Hendelman, 2000). Additionally, the brainstem projects to the prefrontal cortex. This dopaminergic input has been shown to have regulatory effects on the coding properties of the prefrontal cortex (Jacob, *et al.*, 2013; Williams and Goldman-Rakic, 1998).

The prefrontal cortex has connections to all sensory systems as well as the motor systems (Morecraft and Hoesen, 1993; Preuss and Goldman-Rakic, 1989) and the motivational and the reward systems. This gives the PFC its highly associative character and places it at the apex of cortical hierarchy.

1.1.2 Executive Functions

One of the first attempts to pin down the functions of various parts of the neocortex was by Eduard Hitzig and David Ferrier at the end of the 19th century. Hitzig and Ferrier tried to map the functions of different cortical areas by stimulating the brain of a dog with currents. The stimulation of most of the neocortex elicited either stereotypic motor responses or reactions of the animal which indicated sensory perception. The authors failed to elicit any consistent response by stimulation of the frontal lobe of the brain and coined the term “silent cortex” to describe it (Finger, 2000). Although, as discussed above, dogs do not possess the true granular prefrontal cortex of the primates, this finding indicated that the frontal lobe has a more subtle and complex function than just processing sensory input or preparing motor output. Later findings have showed that the PFC plays a role in cognitive and emotional behaviour (Goldman-Rakic, 1987).

In 1931 Jacobsen showed that monkeys and chimpanzees, who could remember a cued food location for up to five seconds, lost this ability after focal frontal lesions (described in Fuster, 2001; Wise, 2008). Thus, it was assumed that the PFC plays a vital role in maintaining information online. In the 80s and 90s a lot of research focused on this hypothesis and working memory was considered, if not the only, but the most important

function of the PFC (Baddeley, 2003; Wise, 2008). In support of this idea, studies have shown that single cells in the PFC, once triggered by an appropriate stimulus, will show an elevated discharge rate while this stimulus has to be remembered by the subject, thus providing information about the stimulus in its subsequent absence (Fuster and Alexander, 1971). This particular discharge pattern was termed sustained firing. More importantly, the PFC has not only been shown to keep the information online, but also to play a role in the protection of relevant information from distortion by distracter stimuli (Malmo, 1942; Sakai, *et al.*, 2002; Suzuki and Gottlieb, 2013).

Though the PFC obviously plays an important role in working memory, with time it became apparent that the functions of the prefrontal cortex are more diverse. Lebedev and colleagues (2004) trained monkeys to remember a cued position but at the same time attend to another position. Under this protocol, a substantial proportion of the recorded PFC neurons were selective for the attended and not for the remembered position. This finding indicates that this sustained activity during the memory delay period may contribute to the process of attentional selection (Lebedev, *et al.*, 2004).

Attention is the process of focusing on one, relevant aspect of the environment, while ignoring the irrelevant distracters. Salient stimuli, such as loud noises or very colourful displays draw the attention of the subjects. This stimulus-driven process is called bottom-up or exogenous attention and it relies on, among others, the parietal cortex. In the top-down processing, the attention is goal-driven, and directed volitionally by the subject towards certain features, because they are relevant for a current task (e.g. metallic glimmer, when looking for keys). This more cognitive kind of attentional selection is mediated by the prefrontal cortex (Buschman and Miller, 2007).

The prefrontal cortex has also been shown to play a role in goal oriented behaviour. Matsumoto and colleagues (2003) trained monkeys to select different actions in different stimulus conditions depending on the expected reward outcome. About 16 % of neurons in the lateral prefrontal cortex and 18 % of the medial PFC were selective for specific reward-action combinations indicating that the PFC plays a role in the process of action selection (Matsumoto, *et al.*, 2003).

An important mechanism of behavioural control is the response inhibition. Response inhibition is defined as the “suppression of inappropriate responses” (Aron, *et al.*, 2004). Early lesion studies have indicated that the frontal lobe might be involved in this process (Battig, *et al.*, 1962; Iversen and Mishkin, 1970). More recent studies have shown specific activation in the ventral lateral PFC to stimuli which elicit two conflicting responses (Hazeltine, *et al.*, 2003). Additionally, single cell recordings inside the principal sulcus revealed units, which discharge selectively in NoGo trials, when the response has to be suppressed in the classical Go/NoGo task (Sakagami *et al.*, 2001).

Successful behavioural control requires not only action selection when the actions and outcomes are clear but also a decision making process, when the alternatives are difficult to distinguish (Ridderinkhof *et al.*, 2004). Different studies on decision making, while using different protocols and procedures, agree on the following vital elements. A decision can be broadly defined as a choice among several alternatives. It is a deliberate choice, in contrast to a stimulus reaction chain. It is goal directed and involves the gathering of evidence (for reviews see: Gold and Shadlen, 2007; Heekeren *et al.*, 2004; Roitman and Shadlen, 2002) in support of various alternatives. Perceptual decisions usually involve choices based on noisy sensory information in detection tasks (“was there a stimulus?”) or discrimination tasks (“what stimulus was it?”) (Gold and Shadlen, 2007). A recent electrophysiological study in monkeys has shown that neurons in the prefrontal cortex code for the monkey’s abstract decision, irrespective of stimulus features or the motor response, thus showing that non-human primates do not necessarily couple their decision making to a certain motor action but are endowed with the capability of abstract representation of decisions (Merten and Nieder, 2012).

Another important prefrontal function is the representation of categorical information. Categories are subsets of stimuli, responses or concepts which, though they might differ strongly, serve the same function. In 2007, Shima and colleagues (2007) trained monkeys to perform motion sequences of two different categories: alternating (e.g. push-pull-push-pull) or paired (e.g. push-push-pull-pull). During the planning of a movement sequence, neurons in the lateral prefrontal cortex differentiated between these two

behavioural categories (Shima *et al.*, 2007). In another study, an adaptation of a delayed match to sample task was used to train rhesus monkeys to discriminate between morphs of cat and dog images. The monkeys learned to associate the stimuli either with the cat or with the dog category as the images ranged from being cat-like to dog-like in various characteristics. Single PFC neurons responded selectively to stimuli belonging to one of the two categories, irrespective of the visual dissimilarity of the displays. Intriguingly, when one of the monkeys was retrained to separate the same set of stimuli into three new categories instead of two, the neurons in the prefrontal cortex adapted their coding properties and now represented the three new categories instead of the two old ones (Freedman *et al.*, 2001). This representation of arbitrary categories clearly emerged in the PFC due to extensive training. In contrast, categories, which are of vital biological importance for primates, seem not to have to be learned. One such “natural” category i. e. faces has been found to be represented in the prefrontal cortex as well (Tsao, *et al.*, 2008).

This extensive, but by no means exhaustive list of prefrontal functions shows why it has proven so difficult for scientists to pin down the main function of the prefrontal cortex, which seems to be activated by a large variety of cognitive tasks. Currently, cognitive or executive control is considered the main function of the prefrontal cortex and the cognitive capacities described above, facets of this cognitive control. There are several models of executive control in existence and in the following paragraphs I will describe two of them.

Over a decade ago, Miller and Cohen (2001) proposed an integrative theory of the prefrontal functions. They postulated that executive control is achieved via a bias signal, which is produced in the PFC. Consider Figure 2, where C1-C3 stand for representation of sensory signals, R1 and R2 for possible motor actions and N1 for a hypothetical PFC neuron. For example, if C2 were the feeling of hunger and C3 the view of food, then the adequate and predominant response R2 would be to approach this food. But if, in addition to C2 and C3, C1 were the vicinity of a predator, then the adequate response would be to flee (R1), despite the temptations of food. The PFC neuron N1 would

participate in both pathways and have information about all present stimuli and would enhance the processing along the appropriate pathway, while inhibiting the others. This process is considered especially important when one of the alternatives is stronger (more salient or habitual) but inappropriate in the current situation (Miller and Cohen, 2001).

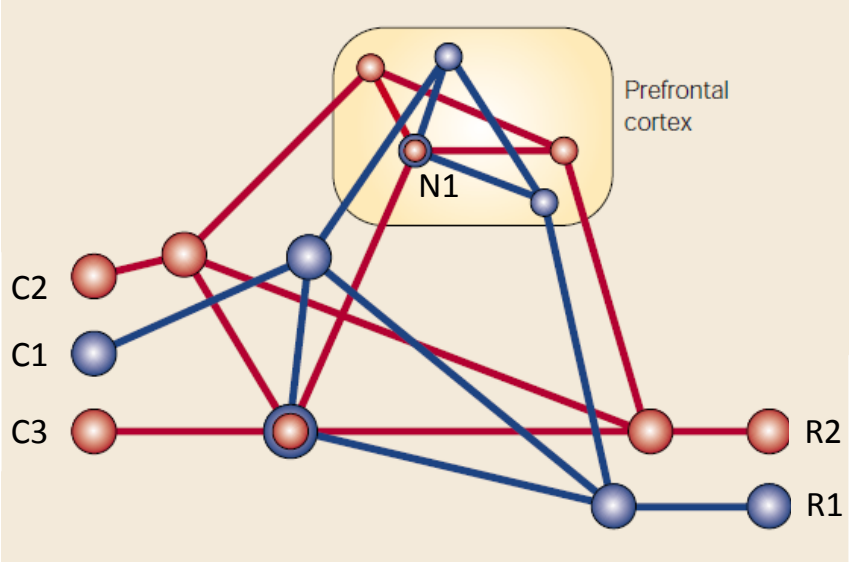

Figure 2: Schematic representation of cognitive control. The same stimulus (e.g. food) elicits different responses (e.g. R1: not approaching, R2: approaching) depending on the context in which the stimulus is presented (e.g. C1: predator in the vicinity; C2: hunger; C3: food). The prefrontal cortex chooses between the different possibilities by biasing one of the pathways. Hence, prefrontal cortex neurons (N1) can be part of different pathways, depending on the context. (adapted from Miller, 2000).

In contrast to this model, Dehaene and Changeux proposed a two-layer cortical hierarchy where the prefrontal cortex neurons represent the “rules of the game” (Figure 3). Level 1 neurons form the input-output layer, which can provide a stimulus-response chain. The second level consists of memory and rule neurons, which switches between the different motor responses (Dehaene and Changeux, 1989).

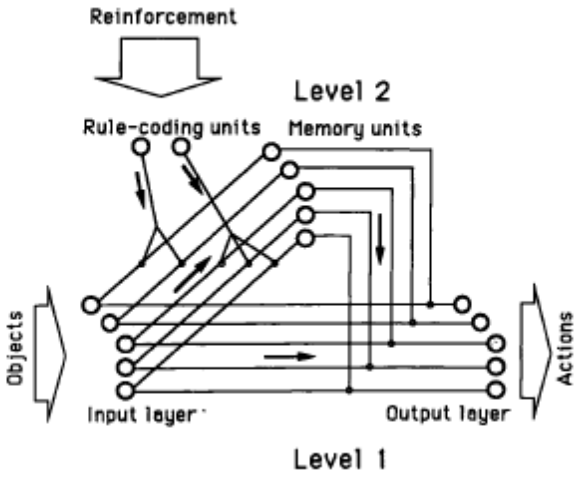

Figure 3: Two-layer cognitive hierarchy. Layer 1 consists of input and output neurons. Their activity is switched on and off by layer 2, which consists of memory and rule-coding neurons. (From Dehaene and Changeux, 1989)

The main difference between those two models lies in the learning process. In the model by Miller and Cohen, the reward signal affects and strengthens the entire network including the PFC neuron and the appropriate sensory and motor representations. At the end of the learning process, the bias signal by the PFC becomes obsolete and gets reduced, as the appropriate action becomes the dominant one (Miller and Cohen, 2001). In contrast, under the assumptions of Dehaene and Changeux, the reward signal strengthens the connections between the rule-coding, the memory and the layer 1 units (Dehaene and Changeux, 1989).

1.2 Magnitudes in the Brain

As described in section 1.1.2, the dorso-lateral prefrontal cortex plays an important role in the representation of categories. One of the most abstract categories are numerosities. Numerosity refers to the number of elements in a set and concern the question “How many?” (Nieder, 2005). Studies in humans and animals suggest that human numerical abilities are based on a phylogenetically older numerical precursor system, which can be found in many different species (Dehaene, 1997; Nieder, 2005). In the following chapter, I will review studies on human numerical cognition, focusing on the non-verbal magnitude system. Following this, I will consider the literature on numerical abilities of animals and the neural representations of numerosities in the brain with a strong focus on non-human primates. At the end of this chapter, I will review some of the literature concerning the representation of other magnitudes in the prefrontal cortex.

1.2.2 Numerosity representation in humans

Human numerical abilities are believed to rely on two separate systems. The language-based precise system and the non-verbal magnitude system. The language-based system is based on our ability to use symbols (i. e. numbers) to represent quantities and operations and enables complex mathematics (Dehaene, 1997). The non-verbal system is thought to be composed of two subsystems: the object tracking and the analogue magnitude system. Object tracking is a mechanism by which each object is represented as an individual, distinct element and is kept within the attentional focus through space and time. A hallmark of the object tracking system is its limited capacity. Only three to four objects can be tracked at a given time. This system seems to be present in both animals (Hauser *et al.,* 2000) and human infants (Feigenson *et al.*, 2002), but its importance is still under debate (Piazza, 2010).

The analogue magnitude system is underlies the language-based numerical representation. In contrast to the latter, the analogue magnitude system is approximate and can be understood as an estimation process. In humans, it is most evident in

subjects who are prevented from counting (Cordes *et al.,* 2001; Merten and Nieder, 2009), in pre-verbal children (Xu and Spelke, 2000) and in humans who lack the symbolic number words. The latter has been shown in works with Amazonian indigene groups. The Pirahã tribe uses a “one-two-many” counting system (Gordon, 2004). The Mundurukú people have numerical words for numbers until five, but only very crude notations above this number (“some”, “really many”) (Pica *et al.*, 2004). Despite their limited ability to enumerate exact quantities, both tribes can compare higher numerosities far above chance. They estimate set size with increasing variability in their estimates as the set size increases. This behaviour shows the characteristic effects of the analogue magnitude system: the numerical size effect, also called the magnitude effect, and the numerical distance effect (Gordon, 2004; Pica et al., 2004). The numerical distance effect was first described by Moyer and Landauer (1967). When subjects were asked to compare two digits, their reactions were quicker when the numerical distance between the digits was large (e. g. the comparison 1 vs. 9 is faster than 4 vs. 5) (Moyer and Landauer, 1967). The numerical size effect was shown by Mechner (1957). When the numerical distance between two numbers being compared was the same, the comparison was easier for smaller numbers than for larger (e.g. 1 vs. 2 is easier, than 8 vs. 9) (Mechner, 1957). These findings suggested that we represent magnitudes on a mental number line, which is compressed for larger numerosities, leading to magnitude perception that is in accordance with Weber’s law (Dehaene, 1997; Shepard, *et al.*, 1975; Whalen *et al.*, 1999).

Early neuropsychological studies showed that the parietal lobe is involved in calculation (Henschen, 1919). Lesions in the angular gyrus led to a deficit termed “acalculia” with patients unable to perform simple calculation tasks. Later studies showed that acalculia cannot be traced towards one single area, but rather seemed to depend on a network, which is composed of parietal (reviewed in Kahn and Whitaker, 1991) and prefrontal regions (Shallice and Evans, 1978). Modern functional magnetic resonance imaging (fMRI) studies showed that both exact and approximate calculations activate the prefrontal and the posterior parietal cortex (e. g. Dehaene *et al.*, 1999; see Dehaene *et al.*, 1998 for a review).

1.2.3 Numerosity representation in animals

The ability to estimate magnitudes is of vital importance for animals in the wild. Knowing if a group of intruding animals is larger than their own or which location has more food sources can be crucial for the survival of an individual. Several studies showed in a conclusive manner that animals use numerical cues in their natural environment (Shettleworth, 2010). The obligate brood parasites, cowbirds, are able to estimate the rate at which their host lays its eggs to find the optimal time for their own egg laying. To do this the cowbirds keep track of the number of eggs added over time and are insensitive to non-numerical cues, such as the total area covered by the host's eggs (White *et al.*, 2009). In another study, lions have been shown to be able to estimate the size of the rival pride by their roars (McComb *et al.*, 1994).

These studies of animals in their natural environment often suffer from methodological shortcomings. In order to assess the animals' numerical competence, it is important to exclude non-numerical cues, such as the density or the total area of the elements, that co-vary with the number which is supposed to be estimated. Laboratory conditions allow these controls. The first researcher who, under controlled conditions, trained different species of birds to discriminate displays with different numbers of dots was Otto Koehler. His birds reportedly mastered numerosities up to six (Koehler, 1941). Later, Platt and Johnson (1971) trained rats to press a lever a required number of times. The number of presses varied between 4 and 24 for different rats. The probability of actual lever presses that the rats made were beautifully described by normal distributions with the peak at the required number of presses. The distributions became increasingly wider, when more lever presses were required. These findings suggest that animals display the same hallmark effects of the analogue magnitude system as humans: the numerical size and the numerical distance effects (Platt and Johnson, 1971).

A major part of the work on numerical cognition and the representation of numerosities in the brain has been done with non-human primates, mostly rhesus monkeys. These studies usually use a numerosity discrimination protocol, instead of sequential counting. A pioneering study was conducted by Brannon and Terrace (1998). They trained rhesus

monkeys to order visual displays with varying sets of objects according to the number of these objects. The displays were varied greatly so that the monkeys could not rely on non-numerical information such as density, shape or the total area of the elements. They were trained to do so with numerosities from one to four. In transfer tasks, the monkeys were able to order numerosities from five to nine, for which they had not received training. Interestingly, the errors the monkeys made were characteristic of the analogue magnitude system. They tended to assess wrongly the order of two numerosities more often if the numerosities very separated by a small numerical distance (e.g. numerosities 3 and 4) than if the numerical distance was larger (e.g. numerosities 1 and 4) (Brannon and Terrace, 1998; Brannon and Terrace, 2000).

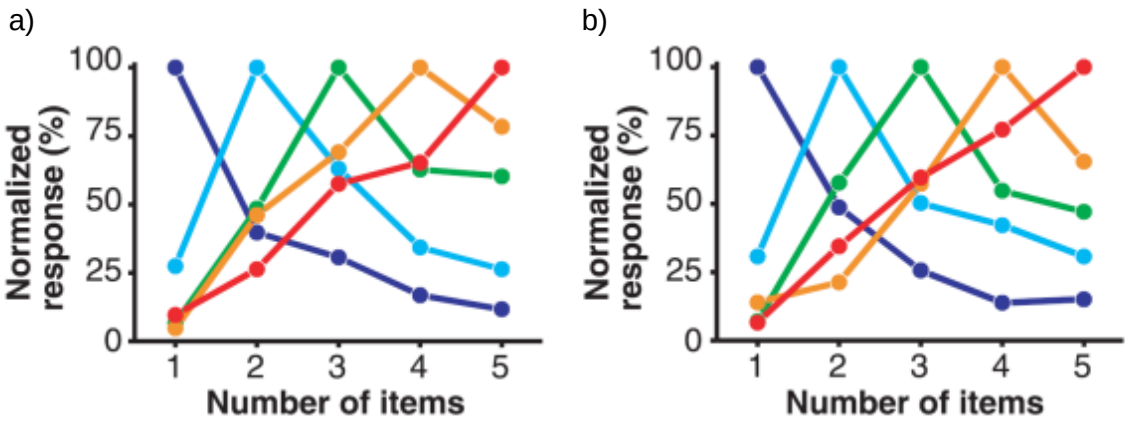

Figure 4: Single neurons in the prefrontal cortex show a tuning to preferred numerosities. The tuning functions are increasingly wider with increasing preferred numerosity. The tuning is slightly asymmetrical, when the curves are plotted on a linear scale. The coding is very similar during (a) the sample presentation and (b) the memory delay period. From Nieder *et al.*, 2002

One of the first studies to investigate numerical representation in the monkey brain was done by Sawamura and colleagues (2002). Monkeys were trained to change their motor pattern after a certain number of repetitions. Neurons in the superior parietal lobule represented the ongoing number of motor actions. However, the numerical information could be confounded by motor preparation and the time spent in motion (Sawamura *et*

al., 2002). One study to overcome these shortcomings was done by Nieder and colleagues (2002). They trained rhesus monkeys on a delayed-match to sample task. The monkeys viewed a sample display with a certain number of dots, retained this information over a delay period and were then required to respond if a test display subsequently presented contained the same number of dots as the sample. A large proportion of cells in the dorso-lateral prefrontal cortex was shown to respond selectively to numerosities, both during the sample presentation and during the memory period. The selective cells were tuned to one numerosity, such that their discharge rates were highest to one preferred numerosity and decreased with increasing distance to that numerosity (Nieder *et al.*, 2002). The same kind of coding was found in response to large visual numerosities (up to 30, Nieder and Merten, 2007) as well as to sequentially presented numerosities, in both the visual and the auditory modality (Nieder, 2012). These findings demonstrate that the PFC encodes the numerosity information in an abstract fashion, irrespective of set size or the manner of the presentation. Single cells signal specific numerosities via a labelled-line code (Nieder and Merten, 2007; Nieder, 2012).

Interestingly, it was not only the behavioural data that showed the distance and the magnitude effect under this protocol, but also the neuronal data. In a follow-up study (Nieder and Miller, 2003) it was shown that the tuning functions of the numerosity selective neurons became increasingly wider with increasing preferred numerosity (Figure 4). Additionally, the left slope of these tuning functions (response to smaller numerosities) was steeper than the right slope (response to larger numerosities). When converted to a logarithmically compressed scale, the tuning functions became more symmetrical and their width (measured by standard deviation) became constant for different preferred numerosities. These results illustrate that numerosities are processed in the brain in accordance to Weber's law, suggesting that sensory and cognitive representations share this coding mechanism (Nieder and Miller, 2003; Nieder and Merten, 2007).

How these numerosity selective cells arise in the visual pathway is still debated. Dehaene and Changeux proposed a parallel numerosity processing mechanism containing four functional layers (Figure 5). Sensory input clusters (e.g. in the retina) encode each object as a Gaussian distribution of activation. In the second layer, on a location map, the objects are encoded as individual activation spots with normalized sizes. The location map units project down to all summation cluster units. These layer 3 units differ in their threshold to activation. When the activation exceeds the threshold, these units respond in a linear fashion to increasing numerosity. Layer 4 contains units responding selectively to numerosity. They receive excitatory projects from one unit of the summation cluster and are controlled by lateral inhibition. This leads to tuning-like responses from the numerosity cluster cells (Dehaene and Changeux, 1993).

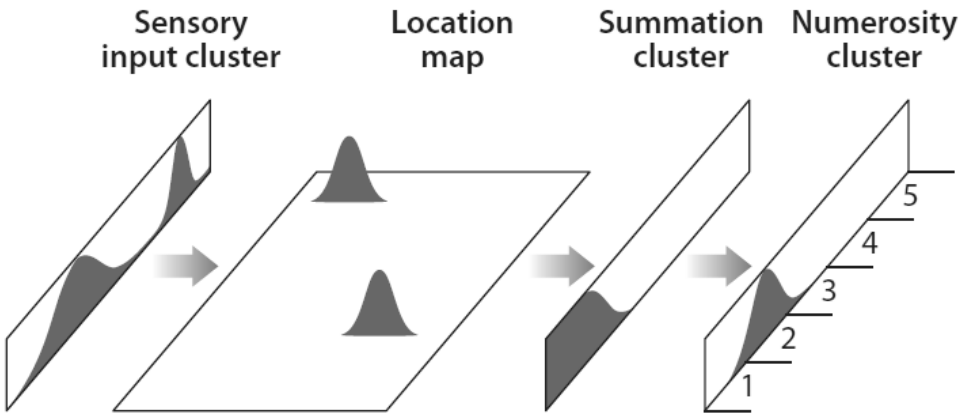

Figure 5: Parallel numerosity detector model. Single elements of a visual numerosity array are first represented as differently sized activation spots, then normalized for size and represented in a summation cluster with increasing activation for increasing numerosity. Finally, lateral inhibition leads to the formation of units with tuning properties, which allow a labelled-line code for numerosities (Dehaene and Changeux, 1993; Figure from Nieder and Dehaene, 2009).

In contrast, Meck and Church (1983) proposed a mode controlled pacemaker-accumulator model. They suggested that every element in a set is added to an accumulator. At the end of the “counting” the accumulator level is read into working memory, where the representation of number is formed. This serial process is analogous to the accumulator model for time processing. The authors suggested that time and numerosity might be processed via the same mechanism on a shared neural substrate (Meck and Church, 1983).

Although numerical information is abstract and extracted from highly variable visual displays, it seems to be extracted in an automatic way. A recent computational study has proposed that numerosity information emerges in deep networks as a statistical property of the image, suggesting the possibility that numerosity is directly processed in the visual system (Stoianov and Zorzi, 2012). Another study showed that numerosity judgments are independent from other visual features such as density or texture (Ross and Burr, 2010). Together with the finding that numerosity estimations are susceptible to adaption just like low-level visual features (Burr and Ross, 2008) and that even untrained rhesus monkeys have numerosity-tuned neurons in the prefrontal and the parietal cortices (Viswanathan and Nieder, 2013), these studies show how fundamental numerical processing is and support the notion of “number sense”. Number sense refers to the idea that humans and animals perceive numerosities intuitively, without any requirement for training. It was suggested, that numerosity is a natural sensory category, which is processed by a hard-wired, designated network in the brain (Danzig, 1930; Dehaene, 1997).

1.2.4 Coding of other magnitudes in the brain

Numerosities are not the only sort of magnitude represented in the prefrontal cortex. Magnitudes can be sensory or more abstract. The frequency of vibrations is represented by tuned PFC neurons, which respond more strongly to one preferred frequency than to adjacent values (Romo *et al.*, 1999; Romo and Salinas, 2003). Weak colour selectivity has also been shown in the PFC (Lara and Wallis, 2014).

The representation of continuous magnitudes such as size and spatial frequencies has also been studied in the PFC. Single cell recordings in rhesus monkeys have shown that PFC neurons are tuned to spatial frequencies and line lengths and represent those magnitudes in a similar fashion as numerosities (Eiselt, 2013; Tudusciuc and Nieder, 2009). However, while one study reported strongly overlapping populations of neurons representing the two magnitude classes (line lengths and numerosities) (Tudusciuc and Nieder, 2009), another reported that the neurons representing the different magnitude classes were intermixed, but the amount of multi-tasking neurons did not exceed the number expected by chance (Eiselt, 2013).

Psychophysical studies in humans also indicate that the processing of number and other magnitudes might be interconnected. In an early study Henik and Tzelgov (1982) showed, that presenting Arabic digits in different physical sizes influenced the speed of numerical size comparisons. The participants took longer to judge physically small, but numerically large digits as being greater than physically large, numerically small digits. Interestingly, this effect was symmetrical such that, when the numerical quantity was irrelevant, it still affected judgement of the physical size (Henik and Tzelgov, 1982). This result has since been replicated with digits and brightness levels (Cohen Kadosh *et al.*, 2008) and numerosities and area (Hurewitz *et al.*, 2006). Physical size corresponds to the space a certain object takes up. The most famous interference effect of number and space is the spatial numerical association of response codes (SNARC) effect. When tested on parity judgments, subjects responded more readily with the left hand for small numbers and with the right hand for larger numbers (Dehaene *et al.*,1993).

Behaivoural interference effects such as described above suggest that two kinds of information are processed, on the same neural substrate. Evidence from fMRI studies shows that different magnitudes are represented in at least partly overlapping regions in the human brain. Pinel and colleagues (2004) have found co-activation in the posterior parietal cortex in luminance, size and numerosity discrimination tasks (Pinel *et al.*, 2004). Another study has shown neural interference in the PFC in time and numerosity judgments (Hayashi *et al.*, 2013).

These results led to the proposition that continuous quantities (size, length, etc.) are processed by the same neural mechanism on the same neural substrate as discrete quantities (numerosities, numbers) (Gallistel and Gelman, 2000). Walsh (2003) proposed a theory of magnitude (ATOM). He suggested that time, space and quantity are part of one magnitude system, which is processed by a parieto-frontal network (Walsh, 2003).

1.3 Aim of the study

The studies described above illustrate that large proportions of prefrontal cortex neurons can be activated by a large variety of tasks, both in humans and monkeys. The encoding strategies that PFC employs are still elusive. John Duncan (2001) proposed the adaptive coding hypothesis, which posits that the neurons in the PFC are not inherently tuned to specific features of the environment, but rather adapt their discharge properties, to code whichever stimulus feature is relevant for the subject. As a result of this property, context-specific parameters shape the tuning functions of PFC neurons (Duncan, 2001). Consequently, changes in the context shift the way stimuli are encoded by single neurons within the PFC network. The support for adaptive coding comes from studies where monkeys learned to categorize stimuli (Cromer *et al.*, 2010; Freedman *et al.*, 2002; Roy *et al.*, 2010) and from decision making tasks (Bongard and Nieder, 2010; Eiselt and Nieder, 2013; Merten and Nieder, 2012; Stokes *et al*., 2013; Vallentin *et al.*, 2012; Wallis *et al.*, 2001)..

However, adaptive coding is only efficient in a very quickly changing environment. Some “natural” categories are always of high relevance for the primates and may possess a privileged position and their neuronal representations could remain in the dedicated network, unaffected by the context and insusepltible to adaptation process. Faces, are such natural category represented in the prefrontal cortex (Tsao *et al.*, 2008).

Numerical quantities are thought to be another natural category (Dehaene, 1997). Animals readily discriminate magnitudes in the wild. In a laboratory setting, when they

are trained to discriminate arrays by colour or shape of the items they also take the number of the items into account, without being specifically trained to do this (Cantlon and Brannon, 2007). These abstract numerical quantities are represented in a dedicated fronto-parietal network. Numerosity selective neurons have been found in numerically naïve monkeys, displaying all the characteristics of those in the fully trained animals (Viswanathan and Nieder, 2013).

Numerosity does not seem to be a learned category, but rather a stimulus feature, which is spontaneously and naturally encoded within visual neural structures of the primate brain. If this is true, numerosity representations are expected to remain unaffected by changes of the magnitude context in which they need to be discriminated. This question is addressed in this thesis. The coding properties of numerosity selective PFC neurons were investigated in different magnitude contexts. Two monkeys were trained on a visual delayed match-to-numerosity task and single-cell recordings were done from the lateral PFC. Within a given recording session, the numerosity task was either presented in isolation (pure numerosity block condition) or embedded in equivalent delayed match to sample tasks with other magnitudes (line lengths and colours) as discriminative stimuli (mixed magnitude block condition). By comparing the proportion and tuning properties of numerosity selective neurons in the respective conditions, we test the outlined alternative coding hypotheses.

2 Materials and Methods

2.1 Animals

The subjects were two adult rhesus monkeys, *Macaca mulatta* (monkey H: 8 kg, monkey L: 7 kg). The monkeys were housed in small social groups. Both animals had experience with colour and numerical stimuli, monkey H also with line stimuli, from previous experiments. All procedures were in accordance with the guidelines for animal experimentation approved by the local authority, the Regierungspraesidium Tuebingen, Germany.

2.2 Experimental Set-up

At the beginning of every experimental session, the monkeys entered their primate chairs (custom build, University of Tuebingen) and were brought into the experimental set-up (Figure 6). The monkeys were placed in a darkened chamber, in front of a computer screen (TFT, 15 inch, Acer AL1511). The distance from the monkeys' eyes to the screen was approximately 57 cm. The monkeys were head fixated throughout the experimental session.

For behavioural responses, the monkeys were trained to use a touch sensitive bar inside their primate chairs. Their eye movements were monitored throughout the experimental session using the ISCAN system (ISCAN Inc., 2006). For reward delivery, a water tube reaching the monkey's mouth was fastened on the primate chair. Visual stimuli were displayed using the two-computer Cortex System (Laboratory of Neuropsychology, NIMH, 2005), which was also used to collect behavioural data. During the recording of neural signals, the Cortex System was connected to the PLEXON system (Plexon inc., 2004) with a parallel port to ensure synchronization of neural and behavioural data.

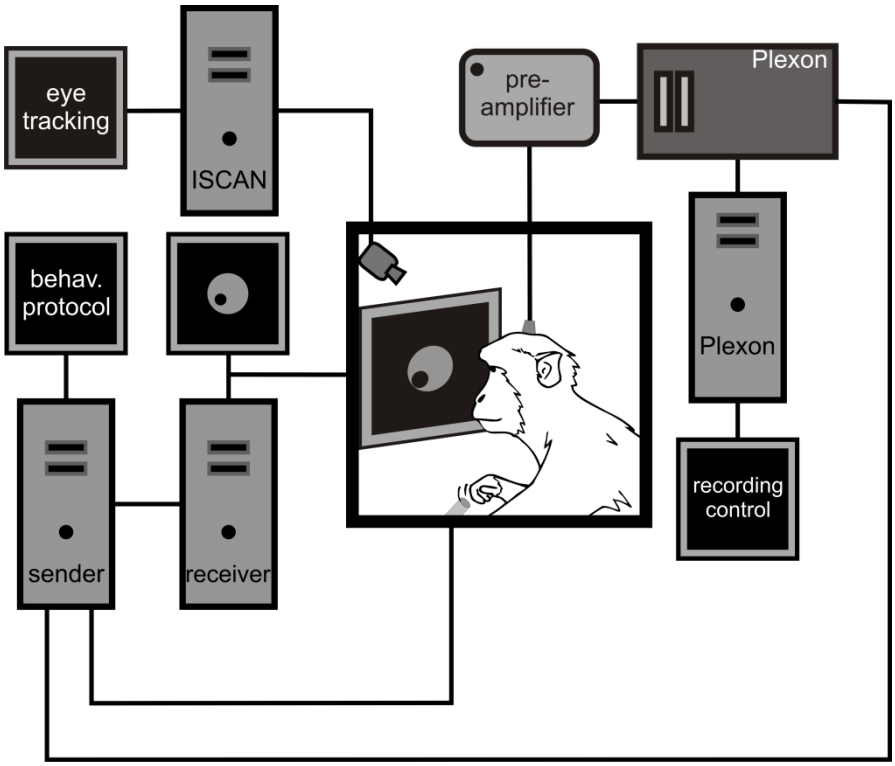

Figure 6: The experimental set-up. The monkeys sat in a darkened chamber in front of a computer screen. They used a touch sensitive bar inside their primate chairs to respond. A two-computer (sender and receiver) Cortex System was used for the acquisition of behavioural data. Eye movements were monitored via the ISCAN infra-red system. The Plexon system was used for single cell recordings.

2.2 Behavioural protocol

The monkeys were trained to perform a delayed match to sample task (DMS) with numerosities, lines of different lengths and colours as stimuli. The trial began when the monkeys grabbed a touch sensitive bar inside their primate chairs and faced the screen. With the start of the fixation period, the monkeys were required to fixate a white dot superimposed on a grey circle (fixation window: 3.5 ° visual angle). After a fixation of 500 ms, a sample, either a numerosity, a line or a coloured ring (example with numerosity two in Figure 7), was presented for 800 ms. During a following 1000 ms delay period, the monkeys needed to maintain fixation and to keep the sample in mind. After

the delay period, a test image was presented. In half of the trials, the first test image (Test 1) matched the sample image and the monkeys were required to release the bar to receive a water reward. In 50 % of the trials, Test 1 did not match the sample. In this case, the monkeys were required to keep holding the bar until after 1200 ms, a second test image (Test 2) was presented, which always matched the sample. Thus, chance performance was 50 % correct trials.

2.3 Stimuli

Three different kinds of stimuli were used: dot numerosities, lines with different lengths and coloured rings (Figure 8). Every kind of stimuli was presented in two protocols: the standard and the control. The control stimulus protocol was used to prevent the monkeys from attending to low-level visual features of the stimuli, which could co-vary with the magnitude of interest (number, length and colour).

Numerosity stimuli were one, two or four black dots superimposed on a grey circle (Figure 8). The individual item's position and size were varied pseudo randomly. The dots in standard stimuli had diameters between 0.55 and 0.95 degrees of visual angle (°VA). The control dots had diameters between 0.7 °VA and 1.55 °VA. In these stimuli, the total area covered by the dots and their density were equalized between the three numerosities.

Line stimuli consisted of horizontal lines of three different lengths (1.125 °VA, 2.625 °VA and 4.5 °VA) which were positioned pseudo randomly inside the grey circle. All the standard lines had the same thickness of 0.26 °VA. Control lines had the same area irrespective of their length and hence, they were varied in their thickness (0.525 °VA, 0.225 °VA and 0.1312 °VA).

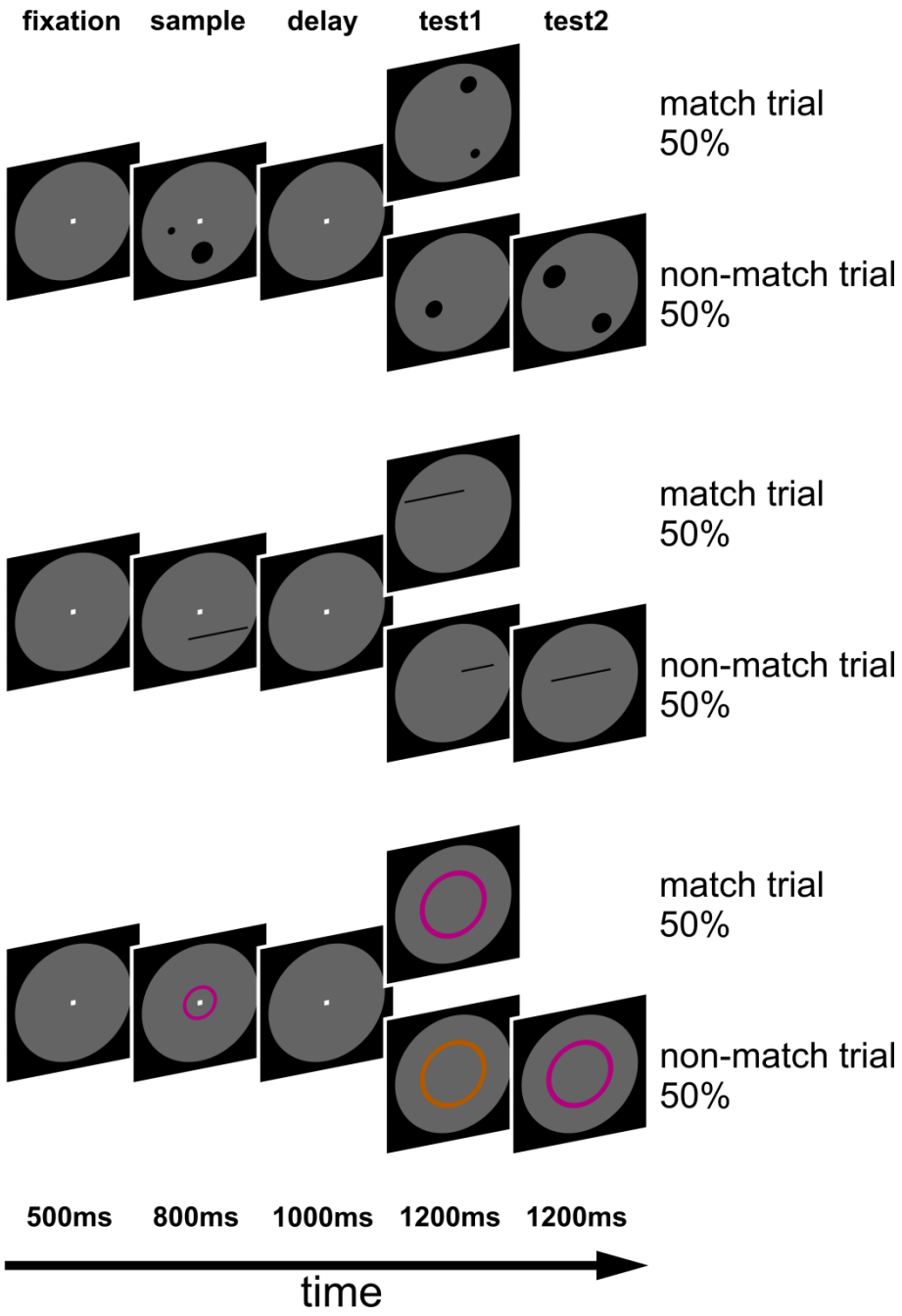

Figure 7: Delayed match to sample protocol. The monkey was required to respond to a test image which matched the sample image and to maintain fixation of the white dot through the fixation, the sample and the delay phases. Three kinds of magnitudes were used: numerosities, line lengths and colours.

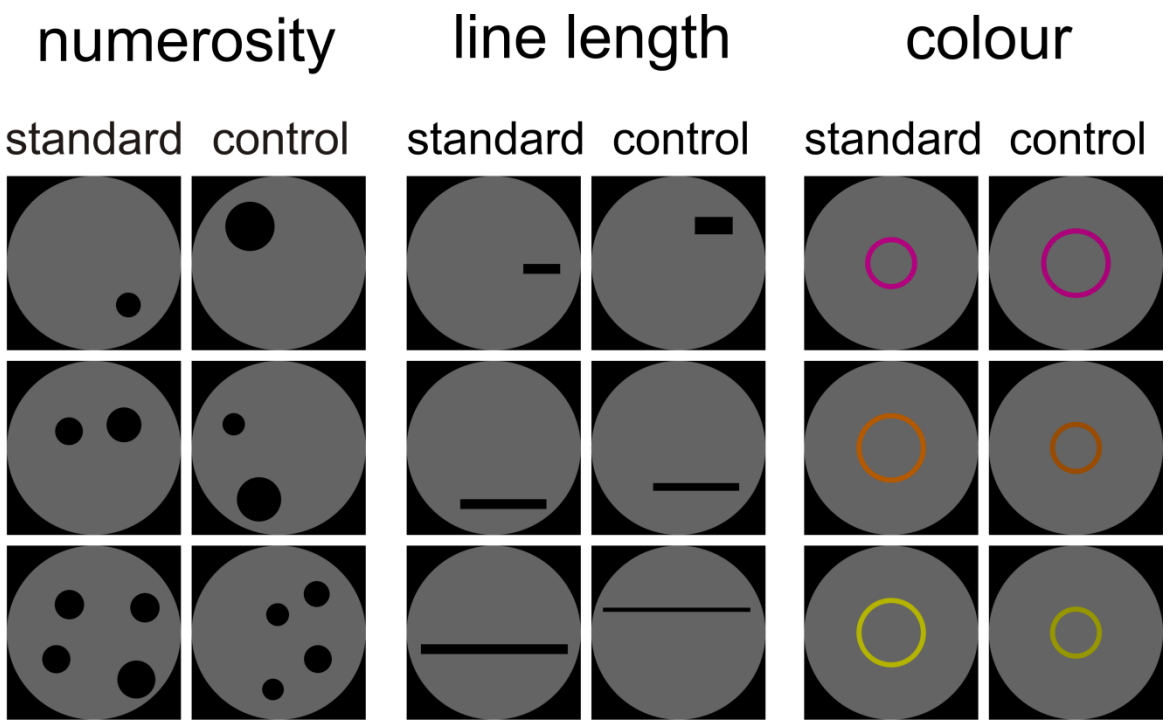

Figure 8: Example stimuli from each set. Left: numerosity stimuli, middle: line length stimuli, right: colour stimuli with example for the two different sizes, small for sample, large for test displays. Left panels of the pairs: standard stimuli, right panels: control stimuli.

The colour stimuli were coloured rings (annuli). They were always positioned in the middle of the grey circle. To prevent adaptation effects on the retina, two different ring sizes were used. Sample stimuli had rings with outer diameter of 1.575 °VA. The rings in test stimuli were bigger and had outer diameters of 2.1 °VA. We used used colours red, orange and yellow. The standard stimuli had bright colours which varied in their luminance (12, 15 and 35 cd/m² respectively). Control stimuli were adjusted to have the same luminance of 10.6 cd/m², measured with LS-100 luminance meter (Konica Minolta).

To prevent the monkeys from memorizing the visual characteristics of the displays, the stimuli (numerosities and lines) with randomized features were generated anew every day (20 images per sample magnitude and stimulus protocol), for each experimental session. For any trial, the sample and test displays never showed the same image. Every

magnitude was presented in a balanced way as sample and as test in control and in standard conditions.

2.4 Procedure

The stimuli were presented in two different trial blocks, the “pure numerosity block” and the “mixed magnitude block” (Figure 9). Each of these blocks was preceded by a short warm-up block, which was later discarded from the analysis. During the pure numerosity block, only trials with numerosity stimuli (both control and standard) were presented. This block contained 48 trials, 16 for each sample numerosity, in pseudo random order. The mixed magnitudes block contained 144 pseudo randomized trials with all three magnitudes as stimuli. Again, 16 trials per sample magnitude were presented.

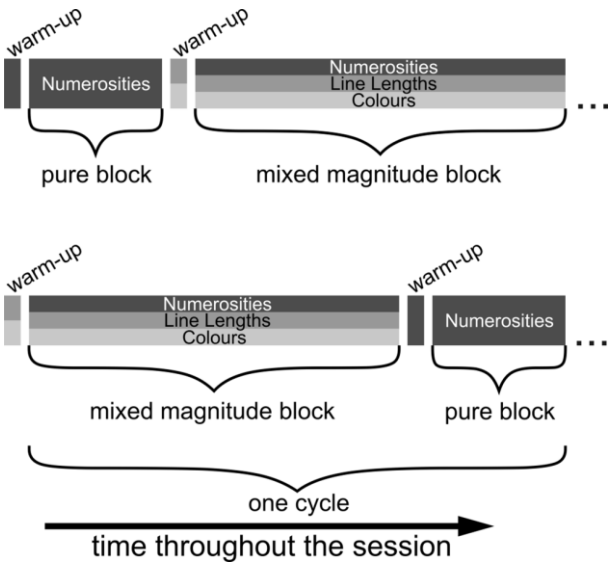

Figure 9: Blocks of different trails within one experimental session. The pure numerosity block contained 48 numerosity trials. The mixed magnitude block contained 144 trials with all three magnitudes. The presentation started either with numerosity trials (upper panel), or with the mixed block (lower penal) on alternating days. The warm-up blocks were used to indicate to the monkey which block was about to start. The monkey was required to complete at least one cycle within one experimental session.

The warm-up blocks had six trials with standard stimuli each. The pure numerosity warm-up block consisted of two trials with each sample numerosity. The mixed warm-up block had three line and three colour trials. The warm-up blocks were used to signal to the monkey whether it had to attend to only the numerosities (pure numerosity block) or to all possible stimulus magnitudes (mixed magnitude block).

To successfully complete an experimental session, the monkeys were required to complete all these four blocks at least once (one experimental cycle). Usually, monkey H completed two cycles and monkey L, three cycles per session. To prevent possible sequence effects, the session started with either the pure numerosity or the mixed block on alternating days.

2.5 Electrophysiological recordings

Before the experiment, the monkeys were implanted with a titanium head bar for head fixation and with a recording well enclosing a trepanation that was located over the right dorso-lateral prefrontal cortex (PFC) and centred over the principal sulcus. All surgical procedures were conducted under general anaesthesia.

Extracellular single-cell activity was recorded using arrays of eight to twelve 1 MΩ glass-insulated tungsten electrodes, which were lowered into the brain for each session. The recorded neurons were not preselected for task selectivity, but only selected for a good signal-to-noise ratio. Signals were amplified and digitized using the Multichannel Acquisition Processor (Plexon Inc.).

All single units were sorted offline using the Plexon Offline Sorter (Plexon Inc.). The action potential waveforms were depicted as dots in a two-dimensional feature space (for example waveform peak against the waveform trough or principal components). Waveforms from a single unit always formed a cluster of dots (Figure 10) which could be graphically encircled and attributed to a specific cell.

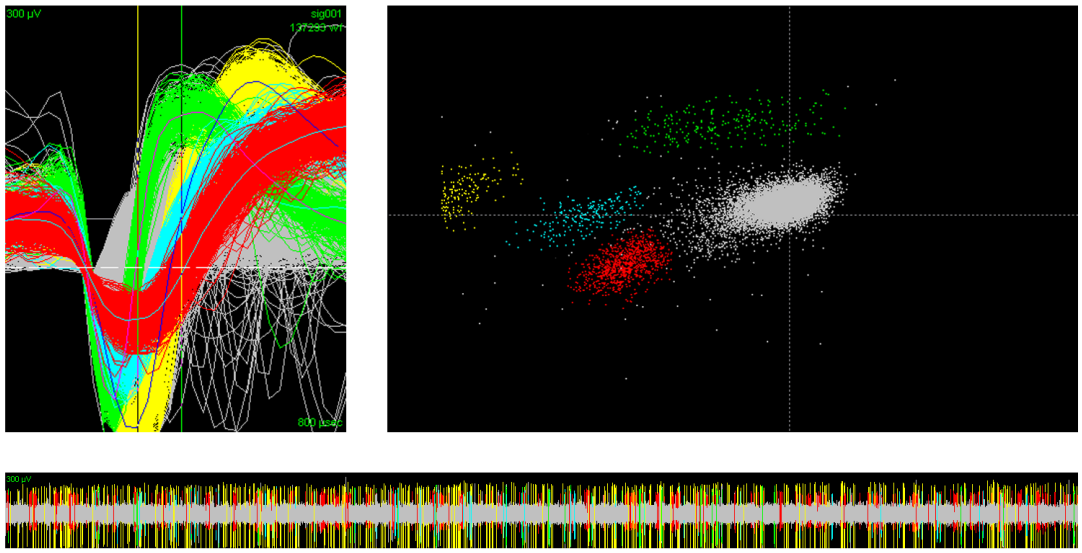

Figure 10: Example session in the Offline Sorter. Left: waveforms aligned by their threshold. Right: the waveforms depicted as clouds in a two-dimensional space, the axes are defined as the first and the second principal components. Bottom: oscillogram, total length 450 s. Yellow, green, blue and red colours indicate the four single units, grey: unsorted noise

2.6 Data analysis

Overall, the two monkeys completed 60 recording sessions (monkey H: 32 sessions, monkey L: 28 sessions). The behaviour was analysed over this entire recording period. The analysis of neural and behavioural data was performed using custom-written MatLab software (version 2011b). Significance level for all tests was $p<0.01$.

Percent correct performance for a given magnitude (e.g. numerosities) was averaged over all sessions. Paired Wilcoxon tests were conducted to compare the performances under the standard and control protocols, for numerosities, line lengths and colours respectively. For comparisons between blocks, the performance was averaged over the stimulus protocol and recording sessions. A two-way ANOVA (factors: sample numerosity and block type) was used for these comparisons.

For neural data, only single units with discharge rates above 1 Hz were analysed, that were present for at least one complete experimental cycle (Figure 9). If a cell was recorded for more than one complete cycle, the additional trials were truncated to have the same number in all conditions. Hence, for a given cell, the same number of trials was analysed for every sample condition. The analysis included only correct trials.

The analysis of the neuronal data was conducted for two time periods, the sample and the delay phase. The sample phase began 100 ms after the sample onset and was 800 ms long. The delay phase was also 800 ms long and began 200 ms after delay onset. The trial-wise average discharge per unit time (discharge rate) was calculated for these periods and used for analysis. To define magnitude selective cells, these data were analysed with 2-way-ANOVAs for the mixed block, with the factors being stimulus protocol and sample magnitude, for numerosity, line length and colour trials separately. A binomial test was used to determine whether the number of multi-tasking units exceeded the amount expected by chance. Numerosity selectivity and block effects were assessed in a separate 3-way-ANOVA with the factors sample size, block condition and stimulus protocol. Cells with a significant main effect of sample size were termed “numerosity cells”. Out of these, cells that showed a main effect of the protocol or interaction with it in either the sample or the delay phase were not analysed further for that phase.

Visual and selectivity latencies were determined for all cells, which were numerosity selective in the sample phase. Visual response latency was defined by the first of five consecutive 10 ms time bins (slid in 1 ms increments) after sample onset where the cell’s discharge rate reached 3 standard deviations (SD) above baseline discharge rate (average activity during the period of 250 ms, starting at fixation onset). Latencies below 50 ms and above 400 ms were discarded. The latency of numerosity selectivity was measured by a sliding Kruskal-Wallis test (kernel width 50 ms, slid in 1 ms increments). Numerosity selectivity latency was defined by the first time bin, at least 50 ms after sample onset, where the test showed significant differences ($p<0.01$) in response to one of the three numerosities.

To analyse numerosity selectivity, tuning functions were created for each cell in the two blocks and the two analysis windows by averaging the discharge rate over the trials for the different sample conditions. The sample magnitude, which elicited the highest discharge rate in a cell, was called the “preferred” sample of this neuron.

A population analysis was conducted with all cells, which were determined as numerosity selective by the 3-way-ANOVA. Population peri-stimulus-time histogram (PSTH) was created using normalized discharge rates (normalization: difference between the base line and the trial discharge rate, divided by the SD of the baseline). For further analysis, numerical distance functions with normalized discharge rates were created (Figure 19). The discharge rate for the preferred numerosity during the pure block was defined as 100 % and the lowest discharge rate as 0 %. Discharge rates to the second preferred sample and all samples in the mixed block were normalised according to these bpunds. These normalized discharge rates were plotted against the numerical distance to the preferred quantity of this cell and averaged over all numerosity selective cells. The numerical distance functions for the mixed and the pure block were compared by a Wilcoxon test for each numerical distance value (significance level was Bonferroni-corrected).

To assess possibly small, subthresholdal effects of block, numerosity selective neurons were assigned selectivity indices for the two blocks. The index was calculated as follows:

$$Ind = \frac{discharge\ rate_{preferrd} - discharge\ rate_{non\ preferred}}{discharge\ rate_{preferrd} + discharge\ rate_{non\ preferred}}$$

To investigate the relationship of selectivity indices for individual neurons during the pure and mixed block, the selectivity of each cell in the pure block were plotted as a function of its selectivity in the mixed block. The distance of the cell to the bisection line was calculated. Cells above the bisection line (higher selectivity in the pure block than in the

mixed block) were assigned negative distance values and cells below the bisection line (higher selectivity in the mixed block than in the pure block) were assigned positive distance values. The symmetry of the distance distribution around zero was assessed by a signed rank test. Hartigan's dip test (Hartigan and Hartigan, 1985) was used to test for bimodality in the distribution.

To further assess possible subtle changes in the coding between the two contexts, two analyses were conducted on the entire set of recorded neurons, not preselected for task relevance. A receiver operating characteristic (ROC) analysis was used for the first analysis. The ROC-analysis quantifies how well the signal distribution is separated from the noise distribution (Green and Swets, 1966). The discharge rates of single neurons on trials with their preferred sample were defined as the signal distribution. The noise distribution contained the discharge rates to the non-preferred numerosity for the neurons. The values of the probability distributions were plotted against each other (signal vs. noise), resulting in the ROC-curve. The area under this ROC curve (AUROC) is a measure of how well the two distributions are separated. AUROC values that are close to one mean a perfect separation of the signal and the noise distributions. AUROC values of 0,5 mean that signal and noise are indistinguishable (Green and Swets, 1966). AUROC values were calculated for each cell in the pure and the mixed magnitude blocks and for the sample and the delay phases separately. The distributions of AUROC values were compared with a paired signed rank Wilcoxon test.

Finally, population dynamics were assessed using a noise correlation analysis. The noise correlation coefficient is a measure of how strongly the fluctuations in the discharge rates of two neurons are coupled, when the influence of the stimulus is excluded. Cells closely connected in a network are expected to have stronger noise correlations than remotely connected pairs. To exclude the influence of the stimulus, the average discharge rates over the entire trial (from sample onset till the end of delay) for each cell and trial were z-scored. For z-scoring, the average discharge rate for each stimulus condition was substracted from the trial-wise data. This difference was divided by the respective standard deviation for each stimulus condition. The z-scored data was pooled over the different sample sizes and compared across the block conditions using

Pearson's linear correlation, for each cell pair. The distributions of correlation coefficients were compared between the two blocks, using a paired t-test.

3 Results

3.1 Behavioural data

Two rhesus monkeys (*Macaca mulata*) were trained to perform a delayed match to sample task (DMS). Different magnitudes were used as stimuli. The monkeys learned to discriminate dot numerosities (1, 2 and 4), the lengths of horizontal lines (1.1, 2.6 and 4.5 °VA) or the colour of annuli (red, orange and yellow). The stimuli were presented in two contexts: either the numerosity trials alone (the pure numerosity block) or with all magnitude trials pseudo randomly intermingled (the mixed magnitude block). Additionally, two protocols of stimuli per magnitude were used: the standards and the controls. In the standard protocol, the magnitude (numerosity, line length and colour) varied at the expense of some co-varying low-level visual features. In the control stimulus protocol, the parameters co-varying with magnitude (density and total dot area for numerosities, total area for line lengths and luminance for colours) were equalized for the different samples.

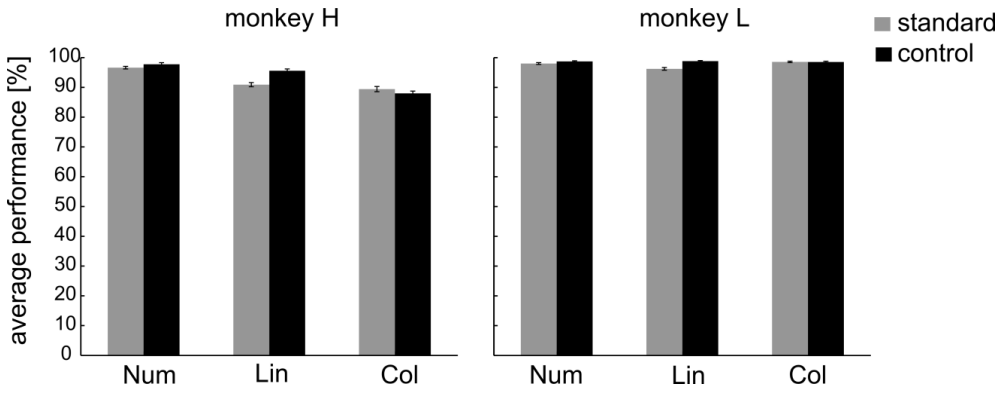

Figure 11: Average performance of both monkeys in the mixed magnitude block under the standard and the control stimulus protocol. Num: numerosity, Lin: line length, Col: coloured rings as stimuli. Chance level: 50% correct. Error bars: standard error of the mean (SEM). n=32 session for monkey H and n=28 sessions for monkey L

The monkeys were highly proficient in this task. The mean performance during the recording sessions was 93.03 % and 98.12 % for monkeys H and monkey L, respectively. Figure 11 shows the average performance of both monkeys during the

mixed block, separated for the three magnitudes and the standard and control stimulus protocols. For both monkeys, the performance was very similar for the standard and the control protocols. A paired Wilcoxon test showed a significant difference between the two protocols for line lengths, but not for numerosities or colours ($T=3.98$, $p=0.0007$; $T=1.65$, $p=0.0998$ and $T=1.17$, $p=0.24$ respectively) for monkey H and for monkey L ($T=4.13$, $p=0.0004$; $T=1.86$, $p=0.0635$; $T=0.27$, $p=0.79$). Despite the significant result, the difference in the performance was very low between the protocols. In line length trials, the stimulus protocol had an effect size of only 4.7 % for the monkey H and 2.6 % for the monkey L, showing that the monkeys were not relying on the low-level visual features for magnitude discrimination.

As there was no significant protocol effect in the numerosity conditions, the data was pooled for further analysis. A comparison between the mixed block and the numerosity block (numerosity conditions only) and the three different sample numerosities (1, 2 and 4) is shown in Figure 12. Both monkeys performed equally well with all three samples (two-way ANOVA, monkey H: $F(2)=2.12$, $p=0.12$; monkey L: $F(2)=0.47$, $p=0.63$). Monkey H performed slightly, but significantly better on trials during the pure numerosity block, than during the mixed magnitude block ($F(1)=7.27$, $p=0.0076$). Monkey L did not show any difference in performance between the two blocks ($F(1)=1.04$, $p=0.31$).

Additionally, the reaction times on match-trials were analysed (Figure 13). Monkey H showed a steady increase in reaction times with increasing sample numerosity ($F(2)=84.9$, $p<0.0001$), and a slight increase of 5 ms from the pure block to the mixed magnitude block. Monkey L, on the other hand reacted faster to the border sample numerosities (1 and 4) than to the middle one (2) ($F(2)=33.6$, $p<0.0001$) but exhibited no difference between the two block conditions ($F(1)<0.0001$, $p=0.42$).

All significant differences had effect sizes below 5 %. Thus, the performance for numerosity trials was comparable in both block types. This indicates that the addition of line and colour trials in the mixed magnitude block did not change task demands for the numerosity trials, but only changed the contextual framework of numerosity discriminations.

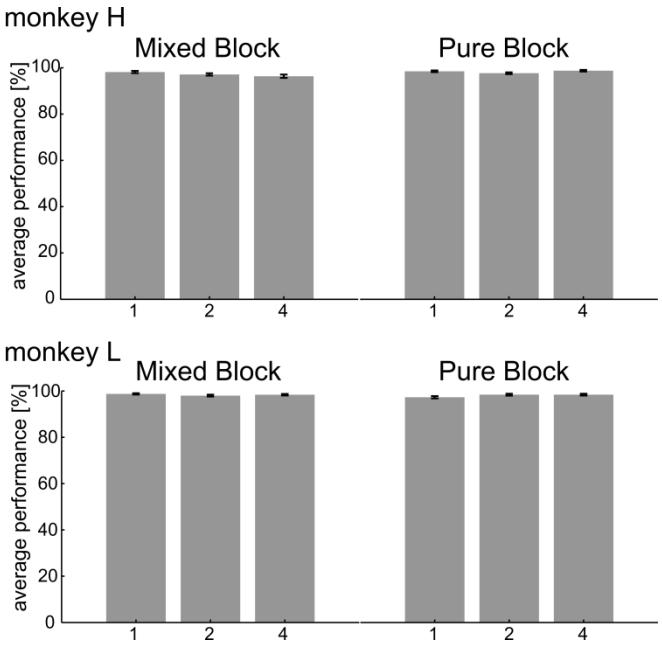

Figure 12: Average performance in numerosity trials, during the mixed magnitude block (left) and the pure numerosity block (right), for both monkeys.

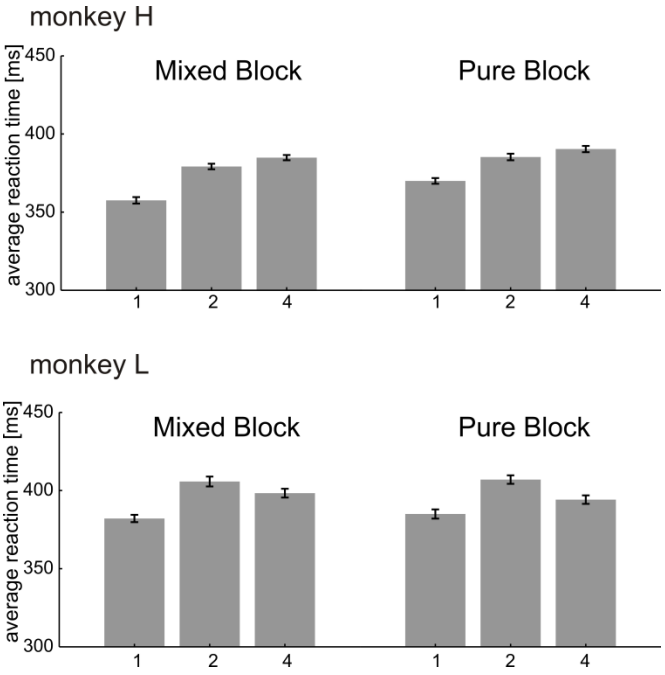

Figure 13: Average reaction times on match numerosity trials, during the mixed magnitude block (left) and the pure numerosity block (right), for both monkeys.

3.2 Coding of Different Magnitudes

In total, 394 single neurons were recorded in the dorso lateral prefrontal cortex (monkey H: 220 and monkey L: 174). The activity of these single cells was analysed in two time windows: the sample phase, beginning 100 ms after the onset of the sample stimulus and the delay phase, beginning 200 ms after the offset of the sample stimulus. Both time windows were 800 ms long. The discharge rates were averaged for these time windows over the relevant trials and analysed separately for the sample and the delay phases.

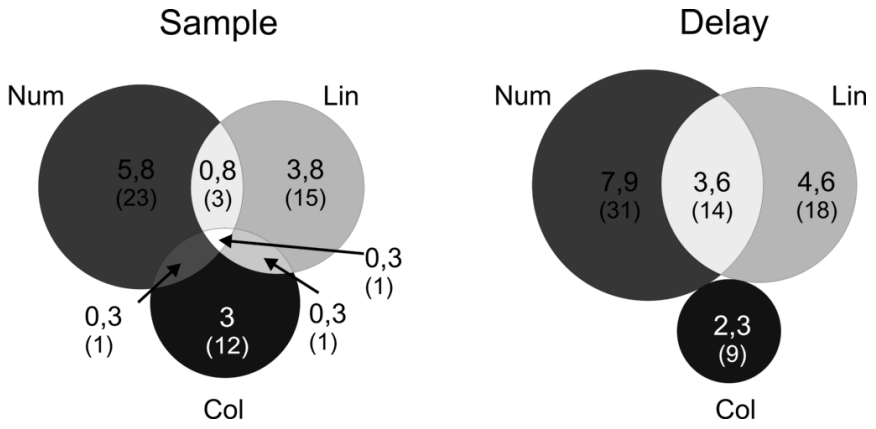

Figure 14: Distribution of magnitude selective neurons in the mixed block during the sample (left) and the delay phase. Most cells were selective for only one magnitude but a few showed mixed selectivity (intersections in the Figure). Large numbers indicate the proportion of selective cells in percent; numbers in brackets are the absolute values.

In the mixed magnitude block, two-way ANOVAs were used separately for every magnitude type to determine whether a cell was selective for this magnitude and the stimulus protocol. A cell was defined as selective if it showed a significantly different discharge rate to one of the quantities as to the others, for each magnitude type (e.g. higher discharge rate for numerosity 2 than for numerosities 1 and 4). Additionally, cells were required to show no significant main effect with the stimulus protocol or an interaction with it (all significance levels: $p<0.01$).

Figure 14 shows the distribution of pure magnitude selective cells for the sample and delay phases. Overall 14.1 % (56/394) of the cells were magnitude selective during the sample phase and 18.4 % (77/394) during the delay phase. During the sample phase an equal number of cells was selective for the three magnitudes (one sample Chi^2 test; $Chi^2(2)=4.10$, $p=0.13$). During the delay, the distribution of the selectivity shifted significantly ($Chi^2(2)=21.19$, $p<0.0001$).A majority of these cells were selective for only one magnitude, a small proportion of cells showed selectivity for two, or even all three magnitudes. The number of multitasking cells in the sample phase was not higher than expected by chance (binomial test, $p>0.01$), but on the other hand, the number of cells encoding both, line lengths and numerosities during the delay phase was significantly higher than chance level (binomial test, $p=0.0003$).

Three example magnitude selective cells are shown in Figure 15. In these delay selective cells, the discharge rate increased in response to their preferred quantity, mainly during the delay phase when the monkeys had to memorise the seen sample. Numerosity and line selective cells often displayed a progressive drop in discharge rates with increasing distance to the preferred quantity. Colour selective cells tended to show a more digital on/off response pattern.

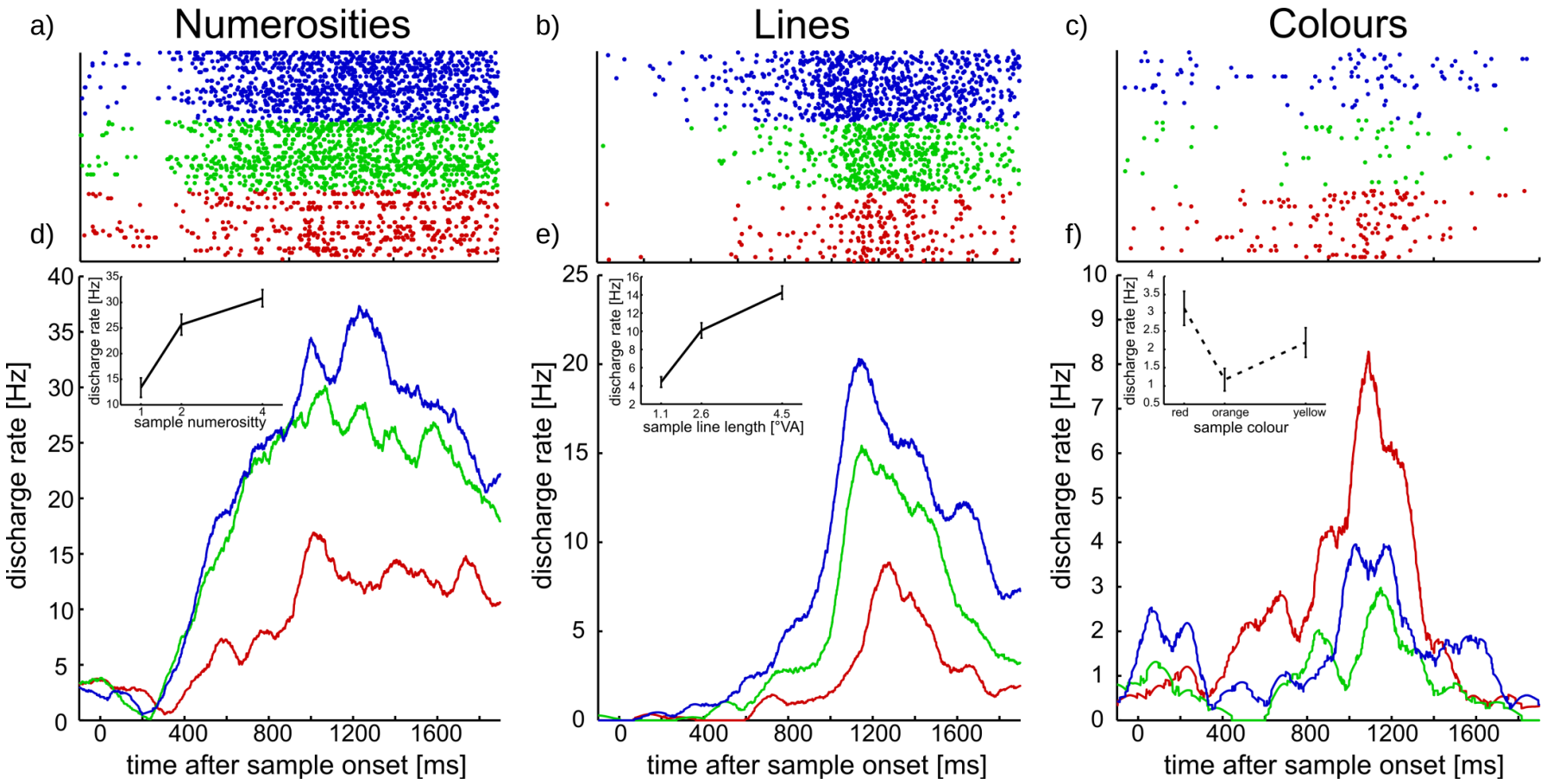

Figure 15: Three example magnitude selective cells for the different magnitudes tested, numerosities (a and d), line lengths (b and e) and colours (c and f). a-c: dot-raster histogram: each horizontal line represents one trial and each dot an action potential. d-f: peri-stimulus-time histograms: average discharge rates over time, smoothed with a Gaussian kernel in a 100 ms sliding window. The plot colours represent the different sample magnitudes (1,2,4 for numerosities, short, middle, long for line lengths and red, orange and yellow for colours). Inserts: average discharge rates for different magnitudes during the delay phase (800-1800 ms after sample onset). The numerosity and length selective cells display tuning properties (decreasing discharge rate with increasing distance to preferred quantity), the colour selective cells did not show these properties. Only trials from the mixed magnitude block are shown.

3.3 Numerosity coding

3.3.1 Single Cells

To assess the effect of magnitude context on the representation of numerosities, discharge rates of individual cells in the numerosity conditions were analysed across “pure numerosity” and “mixed magnitude” blocks, (three-way ANOVA, $p<0.01$, with main factors numerosity, stimulus protocol and block condition). Cells, which only showed a significant main effect of numerosity were called “pure numerosity” cells. All numerosity selective neurons, including the ones which, in addition to the main effect of numerosity, had a main effect of block or an interaction with it, were called “numerosity” cells. Cells, which showed a significant main effect of stimulus protocol or an interaction with it, were not treated as numerosity selective cells.

Figure 16 shows the distribution of numerosity selective cells during the sample and the delay phase for the two monkeys. In monkey H, out of the approximately 7 % numerosity selective cells during the sample phase, 6 % were pure numerosity detectors, without any other main effects or interaction. For monkey L, this proportion was about 12 %. During the delay phase, the proportion of pure numerosity selective cells increased to 13 % in monkey H and 14 % in monkey L.

Whether the monkeys were engaged in the pure numerosity block or the mixed magnitude block, seemed to have little effect on numerosity representation. During the sample phase, only two cells (monkey H) showed a significant main effect of the blocking condition (in addition to the main effect of numerosity). No neurons displayed a significant interaction between the factors block and sample numerosity. During the delay phase, a main effect of block could be found in 3 % of the cells in monkey H and in less than 1 % in monkey L. Two cells (monkey L) showed a significant interaction between the numerosity and the blocking condition. Thus, the context of numerosity discrimination hardly modulated the response properties of the numerosity detecting PFC cells.

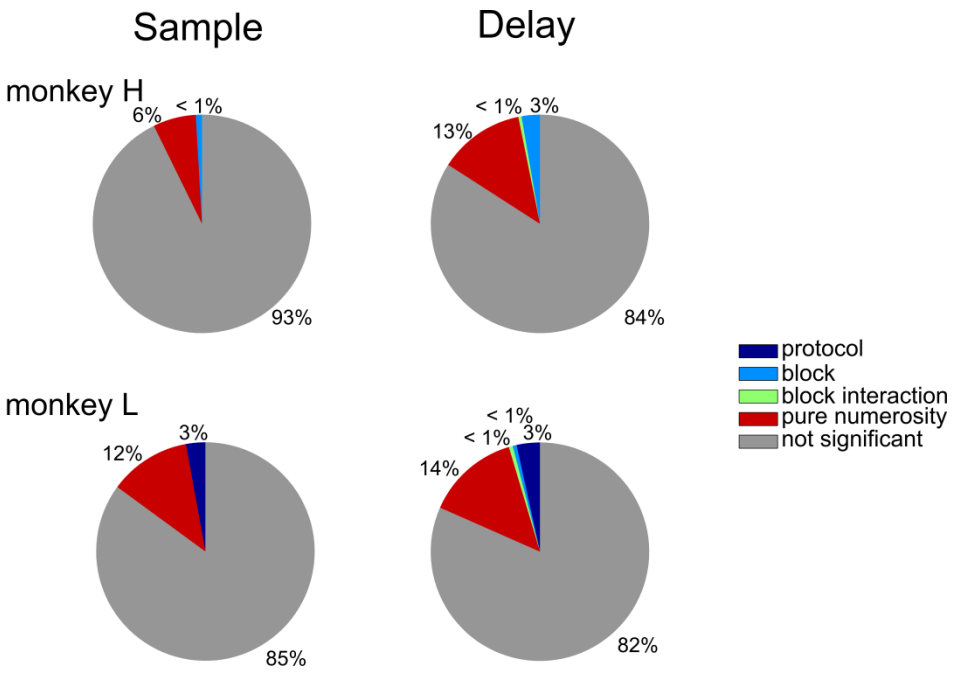

Figure 16: distributions of numerosity selective cells in the sample (left) and the delay (right) phase for the two monkeys. Coloured segments: numerosity selective cells selected by a three-way ANOVA. Dark blue: cells with an additional main effect of stimulus protocol or an interaction with it; light blue: additional main effect of blocking codition; green: additional interaction between numerosity and block; red: purely numerosity selective cells without any other significant interactions or main effects; grey: not selective for numerosity.

Figure 17 shows the response of an example cell, which was purely numerosity selective (no other main effects or interactions) during the delay phase. The peri-stimulus-time-histogram (PSTH) shows the averaged and smoothed discharge rates (Gaussian kernel, 100 ms sliding window) plotted over time. The different colours represent different sample numerosities. The cells that showed significantly different discharge rates to one numerosity than to the others were deemed to be numerosity selective. The numerosity, which elicited the highest discharge rate, was called the “preferred” numerosity of the cell. On average, the discharge rate decreased with increasing distance to the preferred quantity, thus resulting in a tuning curve for each cell. The example cell in Figure 17 showed a preference for the sample numerosity four. This preference was the same in the mixed magnitude block and in the pure numerosity block. Panel e shows the cell’s

tuning curves, which were virtually identical in the pure numerosity and the mixed magnitude block. These results indicate that there was no influence of the blocking condition on the coding properties of single neurons in the prefrontal cortex.

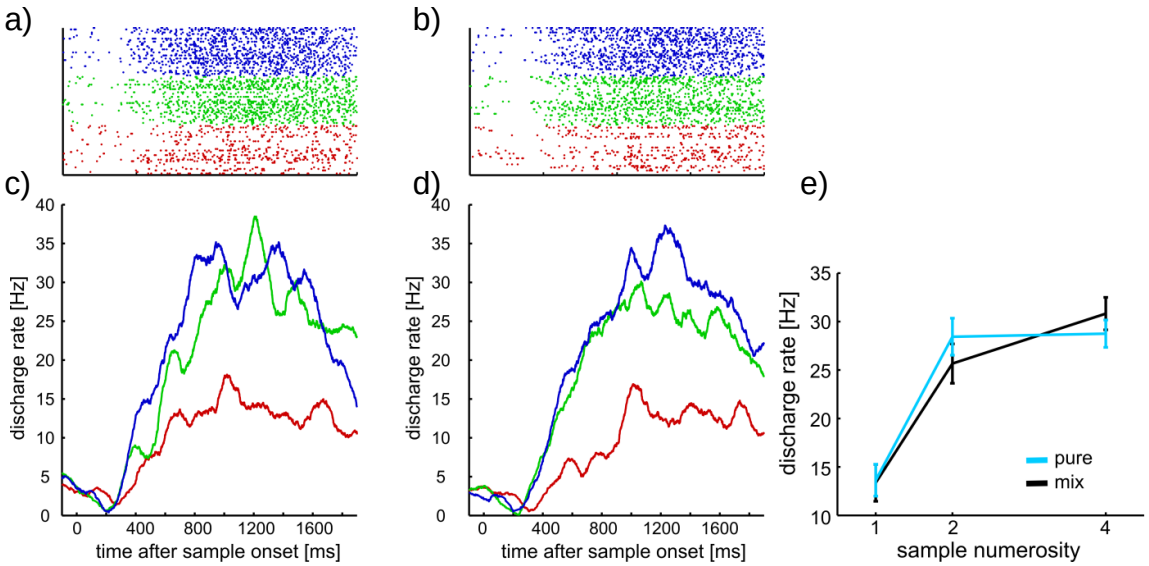

Figure 17: Example sample and delay numerosity selective cell in the pure (a, c) and the mixed magnitude block (b, d), selected by a three-way ANOVA. The cell exhibits very similar responses to different numerosities in the two context conditions. e) Tuning functions in the delay phase. c and d smoothed with a sliding average, using a Gaussian kernel with a width 100 ms.

3.3.2 Population Responses

To assess whether the magnitude context caused changes at the neuronal population level, the temporal and the discharge characteristics of numerosity selective neurons were analysed. To determine whether the time course of numerosity representation was altered as a function of the magnitude context, the visual response and selectivity latencies were calculated for all the cells that were numerosity selective during the sample phase.

The median latency of the visual response was 200 ms in the pure numerosity block and 185 ms in the mixed magnitude block (Figure 18 a). The difference between the blocks was not significant (Mann-Whitney U test, Z=1.07, p=0.29). This indicates a similar onset of a visual response in the two block types.

The latency of numerosity selectivity was defined as the first 50 ms window in which a sliding Kruskal-Wallis test showed significant difference in the discharge rates in response to different sample numerosities. This was done for each numerosity selective neuron during the sample phase. The median selectivity latencies were 299.5 ms for the pure numerosity and 260 ms for the mixed magnitude block conditions (Figure 18 b). There was no significant difference in the onset of selectivity between the two blocking conditions (Mann-Whitney U test, Z=0.76, p=0.491). Hence, the context of numerosity discrimination did not affect the time course of the numerical representations in the prefrontal cortex.

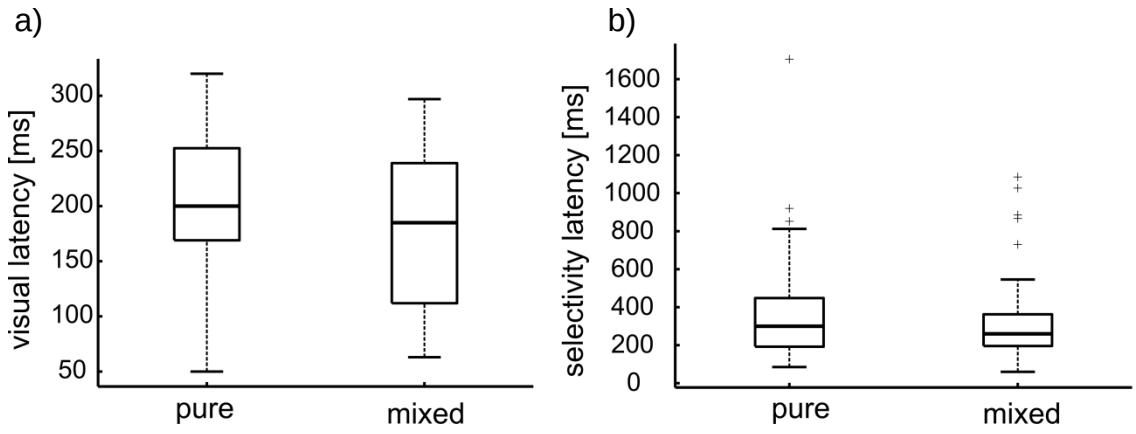

Figure 18: latency distributions of numerosity selective cells. a) Latencies of visual responses, b) selectivity latency, determined by a sliding Kruskall-Wallis test.

Next, the tuning properties of numerosity selective cells in the two different blocks were analysed. Figure 19 shows average peri-stimulus-time histograms of numerosity selective neurons. Panels in a and b show the population responses of sample selective

neurons in the mixed magnitude and the pure numerosity block, respectively. The population responses were very similar in the two contexts. In both blocks, the cells first displayed a clear visual response about 100 ms after sample onset and started differentiating between the preferred and the non-preferred numerosities about 200 ms after sample onset. Delay selective cells (panels d and e) showed similar discharge properties in the two blocks, as well. As a population, they differentiated between the numerosities from the beginning of the delay phase, reflecting the finding that a lot of sample selective cells show the same selectivity in the delay phase (for example: Figure 15).

To assess the sharpness of tuning (e.g. the width of the tuning curve) and thus how well the neurons discriminated between the numerosities in the two block conditions, the discharge rates of numerosity neurons were normalized and plotted against the numerical distance to the preferred numerosity of the cell. The highest average discharge rate during the pure numerosity block was defined as 100 %, the lowest as 0 %. The intermediate discharge rate in the pure block and all values from the mixed magnitude block were normalized relative to these values. These normalized discharge rates were averaged over all cells for the two different blocks (Figure 19 c and f). For both blocking conditions, the discharge rates dropped monotonously with increasing numerical distance from the preferred quantity. The normalized discharge rates in the two blocks were compared separately for each distance to the preferred numerosity. There were no significant differences between the two blocks, neither in the sample nor in the delay phase, indicating the same sharpness of tuning remained, irrespective of the magnitude context (Wilcoxon test with Bonferroni correction, all comparisons $p>0.01$).

To compare the strength of numerosity selectivity, a selectivity index (SI) was calculated for individual neurons in the pure numerosity and the mixed magnitude blocks (Figure 20 a). This index is a measure of how much the discharge rates to the preferred numerosity differ from those in response to the least preferred numerosity. No difference between the blocks in SI values was detected in the sample phase (mean pure numerosity block SI=0.39; mean mixed magnitude block SI=0.35) (Wilcoxon test, $Z=1.24$, $p=0.21$; $n=37$).

Similarly, mean SI values were equal during the delay period for both blocks (mean pure numerosity block SI=0.42; mean mixed magnitude block SI=0.42) (Wilcoxon test, Z=0.23, p=0.82; n=61).

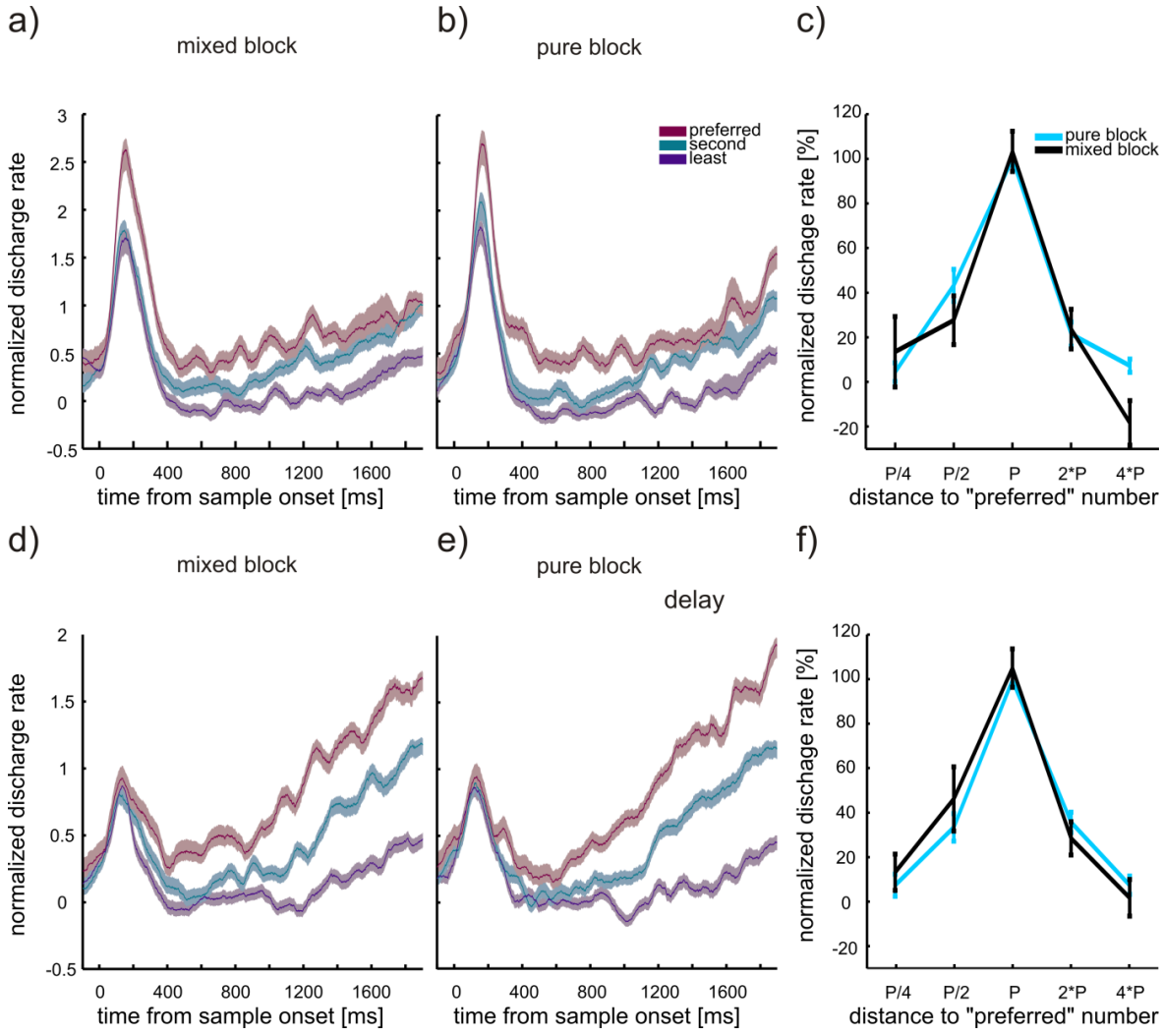

Figure 19: average PSTHs for preferred, second and least preferred numerosities for all cells which were numerosity selective the in the sample (a and b) and the delay (d and e) phase. c and f: normalized response rates of numerosity selective neurons as a function of distance to the preferred numerosity in the pure numerosity and the mixed magnitude block, for sample and delay selective cells respectively. P: preferred numerosity of the respective cell.

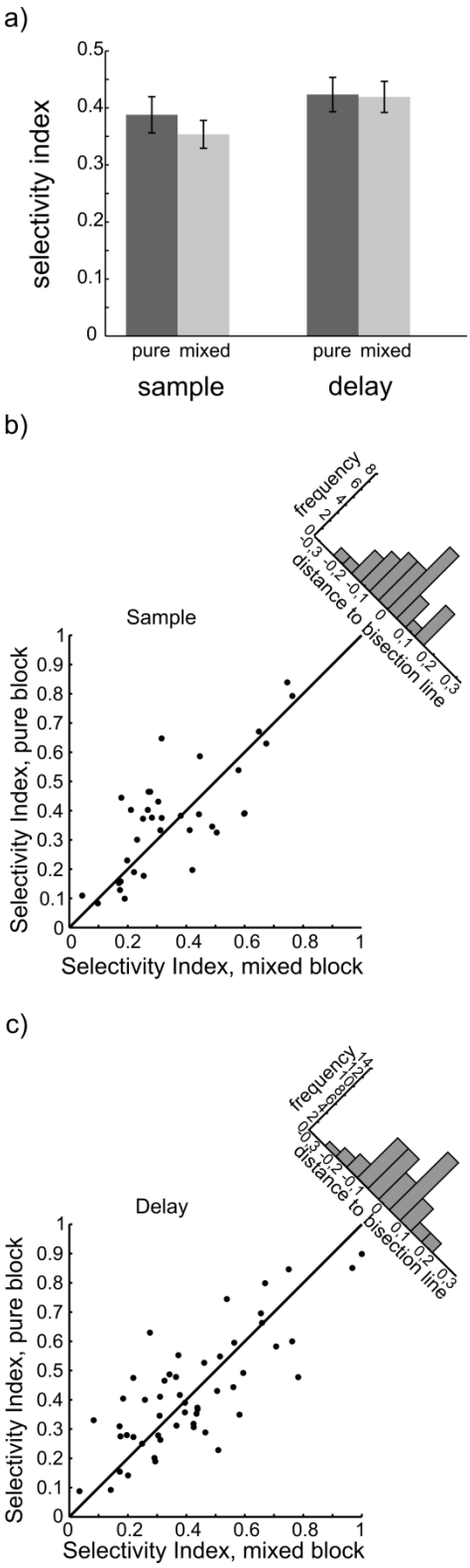

Figure 20: Selectivity in the two blocks. a): Average selectivity indices of all numerosity selective neurons in the pure numerosity and the mixed magnitude blocks. Scatter plot of selectivity indices in the pure numerosity block as a function of the selectivity in the mixed magnitude block in sample (b) and delay selective (c) cells. Each dot represents one cell. Inserts: distance of the dots to the bisection line, positive values were assigned to dots below the line (higher selectivity in the mixed than in the pure block) and negative to the dots above the line (higher selectivity in the pure than in the mixed block)

Even if SI are equal on average, it might be possible that two separate neuron populations react differently in the two blocks, leading on average to indistinguishable differences between blocks. To address this question, the selectivity index in the pure numerosity block was plotted as a function of selectivity in the mixed magnitude block (Figure 20 b and c). The distance of the resulting points to the bisection line was calculated. The distribution of distances is depicted in the inserts. A skewed or a bimodal histogram would suggest two different populations of neurons. Hence, the distribution of distances was tested for symmetry around zero and bimodality. The distribution was not significantly different from a normal distribution, neither in the sample (signed rank test, Z=1.24, p=0.21) nor in the delay phase (signed rank test, Z=0.23, p=0.89). A potential bimodal distribution was tested with the Hartigan's dip test for bimodality (Hartigan and Hartigan, 1985) and was also not significant (sample: p=0.78, delay: p=0.82).

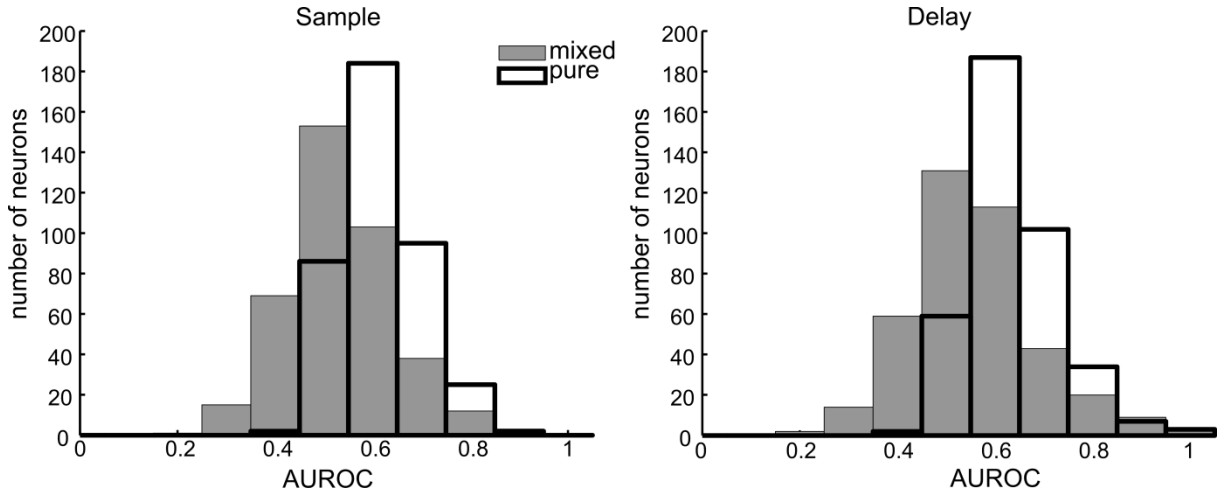

Figure 21: Distribution of AUROC values for all recorded neurons in the pure and the mixed block during the sample (left) and the delay phase (right). Values near 0.5 indicate that a cell did not distinguish between the preferred and the non-preferred numerosity; values close to 1 indicate perfect discrimination. n=394 neurons

Another possible way to detect subtle changes in the tuning properties of the population is to include all recorded cells and not to focus on numerosity selective cells exclusively. This was done using the receiver operating characteristic analysis (ROC). This analysis quantifies how well a cell differentiates between the stimuli and is applicable to the entire neural population irrespective of classical selectivity measures. AUROC values close to 0.5 indicate that a cell does not differentiate between the numerosities and values close to 1 indicate a perfect discrimination.

Figure 21 shows the distribution of AUROC values for all recorded cells during the sample and the delay phase for the two blocking conditions. The average AUROC values in the sample were 0.62±0.0041 in the pure and 0.54±0.0057 in the mixed block and 0.64±0.0046 and 0.56±0.0066 during the delay phase. These differences were significant (paired t-test, $p<0.0001$ for both sample and delay) and were not attributable to simple differences in the mean firing rate (tested using paired Wilcoxon test, $p=0.13$ for sample and $p=0.56$ for delay) thus, indicating a better discrimination between the numerosities in the pure numerosity block than in the mixed magnitude block.

Lastly, the population dynamics were analysed using noise correlations. The noise correlation analysis subtracts the influence of the stimulus from the neural response, leaving only the seemingly random fluctuations in discharge rates. Strong correlations of these fluctuations between neurons are indicative of common input within a neural network. In this study, 896 pairs of simultaneously recorded neurons were analysed. Figure 22 shows the distribution of noise correlation coefficients. The mean of correlation coefficients was 0.023±0.0062 in the mixed magnitude and 0.028±0.0063 in the pure numerosity block, indicating a very low correlation in the general population. There was no significant difference in noise correlations between the two blocks (paired t-test, $p=0.53$).

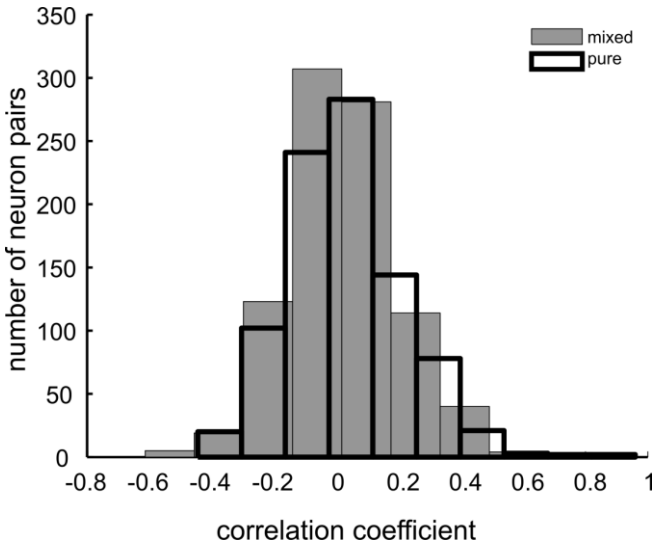

Figure 22: Histogram of the strength of noise correlation in the mixed and the pure block as measured by the Pearson's linear correlation coefficient. n=896 pairs of simultaneously recorded single neurons

Taken together, the neural results show little modulation by task context. There were no differences between the two blocks on the single cell level. The analysis of the population of numerosity selective neurons did not show any differences in the temporal or tuning properties of the neurons. Only when the entire population of prefrontal cortex neurons was analysed, a small increase in the strength of numerosity discrimination was found.

4 Discussion

In this study, a delayed match to sample magnitude task was used to investigate the influence of magnitude context on the coding properties of numerosity selective neurons in the monkey prefrontal cortex. The numerosity discrimination task was presented in two different magnitude contexts. In the pure numerosity block, the monkeys solved the match to sample numerosity task exclusively. In the mixed magnitude block, the numerosity trials were randomly interleaved with match to sample line length and colour trials. Additionally, this design allowed for comparisons between the coding of different magnitudes.

4.1 Task design and behavioural performance

4.1.1 Low-level visual features

In order to ensure that the monkeys were discriminating the intended magnitude dimensions, namely numerosities, line length and colour, and were not attending to low-level visual features, the magnitudes were presented in two stimulus protocol: the standard and the control. Under the standard stimulus protocol the magnitudes were varied at the expense of co-varying low-level features (mainly total stimulus area and luminance). Under the control protocol these low-level features were equalized across sample magnitudes (Figure 8).

Figure 11 shows that the performance of both monkeys was very high (over 90 % in all conditions) and very similar under the two stimulus protocols. The only significant difference between the protocols was found for line stimuli. Both monkeys were better at discriminating control lines than standard lines. The standard line stimuli had the same thickness and, thus, varied in the total area covered by the line. In contrast, the control lines were adjusted in their thickness to have equal total area, irrespective of the line length. The improvement in performance for control lines compared to standard lines is probably due to the additional information in the line thickness, suggesting that the total

area covered by the stimulus is a less salient feature than the line thickness. This effect was very small and low-level visual features did not influence the discrimination of colours and numerosities significantly. These findings are in line with the large body of evidence that show that monkeys readily discriminate magnitudes independent of low-level features (Cantlon and Brannon, 2007; Nieder *et al*., 2002).

4.1.2 Changing magnitude context

The main goal of this study was to investigate the effect the magnitude context had on numerosity discrimination. Usually, the influence of context is studied in task switching protocols. These protocols require the subjects to switch between different rule sets, which are applied to the same stimulus set; for instance, the switching between a match to sample and a non-match to sample task with a given set of stimuli. Often, successful task switching is accompanied by switching costs. Subjects make more errors and/or show greater reaction times on trials directly following a switch than on task repetition trials (summarised in Monsell, 2003). Large parts of the frontal lobe, including the prefrontal cortex were found to be involved in the implementation of the new task set (Dove *et al.*, 2000). Additionally, single cell studies have shown that individual PFC neurons represent task rules in an abstract way (Bongard and Nieder, 2010; Eiselt and Nieder, 2013; Vallentin *et al.,* 2012).

In these studies, the rules of the game change on a trial-by-trial basis, forcing the subjects to view the same stimuli under different task contexts. In the current study, the goal was not to find correlates of the task rules, but rather to see how the context changes the representation of numerosity stimuli. Thus, instead of changing the task applied to the same stimulus set, the task was held constant and the stimulus set was changing. By intermingling the numerosity stimuli with line length and colour stimuli while the task remained to match the various stimuli to the sample, it was possible to change the context of numerosity discrimination without influencing the actual task the monkeys were performing.

In order to keep the monkeys well motivated throughout both blocks, the samples for the different magnitude types were selected to produce the same, high level of performance. As shown in Figure 12, the monkeys performed with high proficiency in numerosity trials in both blocks. Monkey L did not show any differences between the two blocks, neither in the proportion of correct trials, nor in reaction times. Monkey H was slightly better in the pure block, than in the mixed magnitude block, but this increase in performance was accompanied by a slight increase in reaction times as well (Figure 13), indicating a change in strategy. This classical speed accuracy trade-off is well known and has been shown in humans and animals in a variety of tasks (Bogacz *et al.*, 2010; Link and Tindall, 1971; Reed, 1973).

Taken together, these behavioural results showed that monkeys similarly discriminated numerosity in both contexts and were not significantly affected in their performance by the blocking condition. Thus, it was possible to change the context of magnitude discrimination, without affecting the difficulty level of the task at hand.

4.2 Coding of multiple magnitudes

During the mixed magnitude block, the monkeys solved numerosity, line length and colour match to sample tasks. Prefrontal cortex neurons represented all three magnitudes. During the sample phase, the number of selective neurons for the three magnitude types was comparable, but in the delay phase, there were significantly less neurons selective for colours. There was no significant overlap between the three neural populations in the sample phase but in the delay phase 14 PFC cells were selective for both, line lengths and numerosities.

These, somewhat inconsistent results are in line with the current literature. It seems to depend greatly on the experimental environment, whether or not magnitudes are encoded in an overlapping fashion with multitasking cells. Several imaging studies in humans have found co-activation in the posterior parietal cortex (area which involved in

magnitude processing in humans) when subjects discriminated numbers and numerosities or numbers and physical size (Piazza *et al.*, 2007; Pinel *et al.*, 2004). Single cell studies in monkeys have also suggested that quantities, such as line lengths and numerosities, are not only encoded in the same way, but on the same neural substrate (Tudusciuc and Nieder, 2007, 2009). These findings have led to the proposition of ATOM, a theory of magnitude by Vincent Walsh. The theory poses, that all magnitudes are encoded via the same universal magnitude fronto-parietal network in the brain (Walsh, 2003) and thus are sesceptible to interefence effects.

On the other hand some of the described interference effects are asymmetrical; i. e. the interfering influence of one dimension on another is directional and not equal to the reciprocal. This asymmetry was found using a Stroop-like test with line lengths and numerosities (Dormal and Pesenti, 2007). A lesion study with a patient with extensive damage to the right hemisphere, including the inferior parietal and inferior and lateral prefrontal regions, showed that the interaction between numerosity, space and time processing was asymmetrical. While time processing was impaired, numerosity and line length judgments remained unaffected (Cappelletti *et al.*, 2009). Similar effects were found with space and time interactions in children (Casasanto *et al.*, 2010). Another study showed, that while the left intraparietal sulcus seems to be involved exclusively in line length processing, the right IPS is activated by both spatial and numerical magnitudes (Dormal and Pesenti, 2009). A single cell study used the same line length and numerosity stimuli as, described above but in combination with spatial frequencies in a rule switching task. Here again no overlap in the representation of the three magnitudes was found, though the coding properties of the respective populations seemed to be very similar (Eiselt, 2013).

These examples illustrate that it has been difficult to determine the existence of a common magnitude system in the brain. Something similar has also been found with non-numerical categories. Roy and colleagues (2010) trained rhesus monkeys on a match to category task where the animals responded to morphed pictures of cats and dogs. The monkeys were required to switch between two category schemes on a trial-by-

trial basis. One category scheme (A) had the categories “cats” vs. “dogs”, the other one “cat1-dog1” and “cat2-dog2” (B) such that the category boundaries were seemingly arbitrary and had to be learned. The authors found neurons in the PFC, which differentiated either between the categories of the scheme (A) or those of scheme (B). These cells did not multitask and kept their categorical preference on trials, when this information was made irrelevant by the presence of an alternate category cue (namely representation of category scheme A, when B was cued) (Roy et al., 2010).

On the other hand, when the monkeys switched between categorizing cats vs. dogs and categorizing sports cars vs. Sedans in a similar setting some of the prefrontal cortex neurons did multitask and switched from encoding one category set to the other on a trial-by-trial basis (Cromer *et al.*, 2010). Thus, it seems that the prefrontal cortex uses multitasking cells, when two independent category sets have to be encoded, but when the category sets are similar and depend on the same stimulus set, two independent PFC populations emerge to prevent interference effects.

These findings suggest, that whether or not the prefrontal cortex employs overlapping populations for encoding categories, strongly depends on the given task. It seems reasonable to assume that greater task demands, when the monkeys have to switch between categories based on the same stimuli (Roy *et al.*, 2010), promote the employment of distinct neural populations, in contrast to easier tasks with two independent categories (Cromer *et al.*, 2010).

Perhaps the same holds true for magnitudes. In easier tasks, where only two independent magnitudes were used, PFC cells encoded line lengths and numerosities simultaneously (Tudusciuc and Nieder, 2007, 2009). In the current study, with a more complex task with three magnitudes, such multitasking cells could only be found in one task epoch. In another complex task, with three magnitudes and changing response rules, no such multitasking cells were found (Eiselt, 2013).

However, it remains unclear whether numerosities are encoded in a stable way while other magnitudes co-activate the numerosity network when necessary or whether the

prefrontal cortex neurons also change their numerosity encoding properties as a function of the context.

4.3 Stable vs. adaptive coding of numerosities

As seen above, numerosity encoding cells sometimes also encode other magnitudes and at other times do not. Does this influence how the numerosities themselves are encoded by the prefrontal neurons? This question will be addressed in this chapter. Two possibilities have been outlined in the first chapter of this thesis: the adaptive coding hypothesis and the stable coding in number sense.

The adaptive coding hypothesis was proposed by John Duncan and posits that prefrontal cortex neurons have the ability to encode any relevant feature of the environment and change their coding properties to adapt to changing demands. Within this framework, it is to be expected that numerosity encoding is influenced by the context of magnitude discrimination. Support for this hypothesis comes from studies with complex behavioural protocols, showing dynamic response properties of PFC neurons, which are not specialized for a single function but are highly adaptive (Stokes *et al.,* 2013). Selectivity for arbitrary visual categories often emerges after explicit training to distinguish those categories. For example, Freedman and colleagues (2002) showed that monkeys trained to discriminate computer-generated stimuli into “cat” and ”dog” categories had PFC neurons selective for both categories. Subsequently, one of the monkeys was retrained to assign the same stimuli into three new categories (with the two new category boundaries orthogonal to the original two-category boundary). After this learning process, tuning to the previously learned, now-irrelevant, “cat” and “dog” categories was lost. Instead, information about the three-category scheme was evident in the population of PFC neurons (Freedman *et al.*, 2002). Accordingly, it might be expected that PFC neurons change, at least to some extent, their tuning to numerosity and split or adapt their coding capacities according to the different magnitude contexts at hand. After all, encoding and switching between three magnitudes (numerosity, length and colour) in one block requires three times more coding capacity than representing only one quantity (numerosity).

While learning requires plasticity in the response properties of neurons, ubiquitously changing the selectivity of PFC neurons may not be the best computational strategy for all types of abstract information. Data from the literature suggests that numerosity representations in the PFC rely on a sparse code (Olshausen and Field, 2004).

Alternatively, numerosities might be one of the natural categories, which are so important to primates that their coding is stable and unaffected by the environment. Stanislas Dehaene proposed the existence of a number sense. This hypothesis posits that visual numerosity-selective neurons may develop spontaneously and naturally within visual neural structures of the primate brain and that numerical information is encoded in a designated fronto-parietal network (Danzig, 1919; Dehaene, 1997). Support for this idea comes from the recent finding of numerosity-selective neurons in numerically-naïve monkeys (Viswanathan and Nieder, 2013). Neurons in the lateral PFC reliably encode the number of visual items in numerically-naïve monkeys, i. e. monkeys that have never been trained to discriminate numerosity. Based on their psychophysical findings, Burr and Ross (2008) suggested visual numerosity as a sensory attribute because perceived numerosity is susceptible to adaptation just like colour, contrast or speed (Burr and Ross, 2008). It is, however, difficult to imagine numerosity to be represented at the level of the early visual cortex. There is indication that adaptation processes are not restricted to primary visual attributes, but also observed for high-level visual categories such as faces (Webster and MacLeod, 2011). Such adaptation processes suggests a specialized neural pathway with a limited number of units, which are recruited by the adaptive stimulus and are biased by it when the stimulus changes. Numerosity, being subject to adaptation process, could be a natural category encoded spontaneously and stably within dedicated pathways.

To disentangle those two coding possibilities, stable and adaptive numerosity coding, a delayed match to sample task was used in two contexts. In the pure numerosity block, only numerosity trials were presented and in the mixed magnitude block, line length and colour match to sample were added to the numerosity match to sample trials.

If the prefrontal cortex does indeed follow the adaptive coding hypothesis, then in order to deal with increased coding demand in the mixed magnitude block, a single neuron might have to represent more than one magnitude simultaneously and become multitasking (Cromer et al., 2010). Alternatively, cells might switch from encoding line lengths or colours to encoding numerosities in the pure numerosity block, leading to an increased number of selective cells in the pure block. This was tested with a three-way ANOVA. Cells, which change their preferred numerosity or the strength of their selectivity (i. e. selective vs. not selective) would show an interaction between the main factors, numerosity and blocking condition. As depicted in Figure 16 this was the case for very few cells. A vast majority of PFC neurons showed stable preference (Roy *et al.,* 2010) for a specific, preferred numerosity, irrespective of the magnitude context.

Alternatively, under adaptive coding, a single population of neurons could have decreased the strength of their numerosity coding as a function of the increased stimulus space in the three-magnitude block condition. This was observed by Meyer and colleagues (2011), who examined the spatial and shape selectivity of neurons in the prefrontal cortex after training monkeys in various working memory tasks. Neurons were sampled during a spatial working memory task, a feature working memory task, and a spatial-feature conjunction working memory task. Relative to the selectivity found in the feature working memory task alone, the average neuronal selectivity decreased in the conjunction task (requiring both feature and spatial working memory).

There were no differences in the temporal evolution of selectivity (Figure 18) or in the width of the tuning curves (Figure 19). The selectivity index (ratio of discharge rates to the preferred and the non-preferred samples) of individual numerosity selective neurons remained unchanged between the pure numerosity block and the mixed magnitude block (Figure 20). Thus, in contrast to simple spatial or feature discrimination task, the strength of numerosity representations remained stable irrespective of task context.

Lastly, because the changes of coding properties could happen not on the level of single independent numerosity detecting neurons, but in a correlated fashion within the whole population. We examined this with an ROC and a noise correlation analysis. Classically,

the selectivity of a cell for a certain stimulus feature is detected with a statistical test, such as an ANOVA. Units, which fail to reach the significance criterion, still may carry some information about the presented stimuli or the task. To assess these subthreshold effects, a receiver operating characteristic analysis was conducted with the entire population of recorded prefrontal units. During the pure block, the AUROC values were higher than in the mixed block condition i. e. the population of prefrontal cells discriminated between the respective preferred from the non-preferred numerosities better in the pure than in the mixed block. This might be due to a contextual modification of the visual responses or indicate that, to some small extent, the magnitude context may influence the properties of even those cells that show only weak encoding of numerosities. Maybe, cells, which differentiated strongly between numerosities, could not be affected as strongly by the blocking condition, because their coding was already optimal while cells, which had only very weak numerosity effects or none at all could be enhanced by the context of magnitude discrimination.

Our second analysis, noise correlation is a measure for local, transient connectivity between pairs of cells. This connectivity changes as a function of task demands or encoded properties (Aertsen *et al.*, 1989; Palm *et al.*, 1988). Thus, it was hypothesized that the connections between neurons might be influenced by the changing stimulus space (one vs. three kinds of magnitudes in the pure and the mixed block). However, this was not the case. As shown in Figure 22 , the general noise correlation was rather weak and did not differ between the two blocking conditions. This indicates that the connectivity patterns stay stable, irrespective of magnitude context.

In summary, this thesis shows that the magnitude context had a small effect on the discharge properties of numerosity selective neurons in the prefrontal cortex. Neither the sharpness of selectivity nor its time course was affected by the context of numerosity discrimination. To further test the notion of stable numerosity coding in PFC, it will be necessary to investigate the tuning properties of numerosity detectors in more radically changing contexts, such as genuine task switching protocols. For instance, it would be interesting to see whether or not switching from a delayed match to numerosity task

(Nieder et al., 2002; Nieder and Merten, 2007) to a rule switching task based on numerosities (Eiselt and Nieder, 2013; Vallentin et al., 2012) would modify the coding properties. In addition, it remains to be investigated whether long-term learning modifies the proportion or tuning functions of numerosity selective neurons.

5 Summary and Conclusion

In this thesis, the effect of magnitude context on the representation of numerosities was investigated. Additionally, the coding of different magnitudes was compared.

The coding of numerosities was compared under two different blocking conditions. The magnitude context had very little effect on the coding properties of prefrontal cortex neurons. The behaviour of numerosity selective cells did not change with the context. These findings are in line with the notion of number sense. Only weakly numerosity coding cells seem to be enhanced in function during the pure block.

In a second step, we found that sensory and abstract magnitudes such as colour, line length and numerosities are encoded in a similar way in the primate prefrontal cortex. Selective cells display tuning curves when discriminating between different stimuli. The ATOM hypothesis suggests that the brain has a circuit dedicated to the task of representing different kinds of magnitudes. The experimental data so far, however, is ambiguous in this respect. Some studies find significant overlap in the representation of magnitudes; others find asymmetrical interference effects or no overlap at all. Similarly, the data in this study reveal an inconsistent overlap in the populations coding for the different magnitudes, suggesting that the recruitment of multitasking cells depends on the current task and its demands.

Taken together, these two results suggest that numerosities are indeed encoded spontaneously and naturally by a designated network. However, in addition to this population, there might be cells, which can adaptively code for numerosities and other magnitudes as well when recruited under certain conditions.

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