

Temporal Dynamics of Cortical Adaptation

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Abstract

Adaptation of cortical neurons in response to prior stimulus history and the time-course of recovery from adaptation were investigated at the level of action potentials using the juxtacellular single-cell loose-patch recording paradigm in the barrel cortex of juvenile rats. An experimental protocol that paired adaptor and test deflections of the principal whisker for a given neuron was applied in two phases of the study. Experiment 1 involved two adaptor conditions, differentiated by the duration of the adaptor stimulus, presented with a limited range of four adaptor-test temporal separations. Experiment 2 involved a single adaptor condition followed by an expanded range of adaptor-test temporal separations. Experiment 1 demonstrated that the time-course for recovery from adaptation was dependent on the duration of the adaptor stimulus. Experiment 2 demonstrated that recovery of action potential responses in the cortical population follows a sigmoidal pattern, in contrast to the exponential decay of adaptation at the post-synaptic potential level. Data from both experiments provided evidence for adaptation increasing trial-to-trial variability of neuronal responses to stimuli as well as reducing discriminability between the presence or absence of a test stimulus of similar characteristics to the adaptor stimulus. Morphological recovery was achieved for a sample of neurons, and case studies of the relationship between neurons' morphology and functional behaviour provide insights for further investigations into adaptation and functional diversity within the cortex.

Thesis Outline and Research Questions

The objective of this document is to provide a scholarly contribution furthering knowledge of sensory adaptation in the neocortex, with particular focus on the following questions:

- What is the general time-course for recovery from adaptation in the barrel cortex at the action potential level?
- How is the time-course of recovery dependent on the intensity of the adaptor stimulus?
- How are the morphological and laminar characteristics of a neuron related to its adaptation behaviours?

In order to provide appropriate context for this enquiry, Chapter 1 provides a general overview of relevant knowledge, with the first section describing the function and structure of the barrel cortex and the second section describing findings concerning sensory adaptation in the barrel cortex and in other sensory cortices. Chapter 2 describes the methods used in this exploration with sufficient detail as would allow replication. Chapters 3 and 4 describe Experiments 1 and 2 respectively, with each including discussion as to how the findings relate to the research questions. Chapter 5 provides general conclusions as they relate to the research questions and provides further research directions that would more fully answer the research questions.

Background Information

Introduction

One of the critical functions of the mammalian nervous system is the gathering and processing of sensory information about the environment for the purpose of generating behaviour, here understood as actions carried out in the external world. How do single neurons or neuronal ensembles encode sensory stimuli and process them for decision-making purposes? Whisker touch is the rat's primary sensory system for exploring the location and physical characteristics of objects in its environment, with texture discrimination capabilities rivalling human fingertips (Burn, 2008; Diamond *et al.*, 2008; Prescott *et al.*, 2011; Diamond and Arabzadeh, 2013). Rats' whiskers play a critical role in tasks such as distance determination (Schiffman, *et al.*, 1970; Brecht *et al.*, 1997; Krupa *et al.*, 2001), tactile discrimination (Guió-Robles *et al.*, 1989; Carvell and Simons, 1990; Arabzadeh *et al.*, 2006), predation (Gregoire and Smith, 1975; Favaro *et al.*, 2011), and conspecific social contact (Bobrov *et al.*, 2014).

Basic Circuitry

The *whisker-barrel* pathway begins with the whiskers, or vibrissae, which may be actively whisked across a surface or held stationary for the detection of environmental vibrations. Whisking frequencies can vary between 5 to 25 Hz, depending on the sensory task at hand (Carvell and Simons, 1990; Berg and Kleinfeld, 2003). Whisking is carried out via specialised musculature of the mystacial pad (Haidarliu *et al.*, 2010) which receive positive feedback from brainstem on whisker contact with external objects (Nguyen and Kleinfeld, 2004). Kinetic information from the vibrissae is transmitted to receptors in the whisker follicles, densely innervated tactile organs in the mystacial pads equipped with multiple specialised nerve endings (Ebara *et al.*, 2002; Whiteley *et al.*, 2015), which transduce this

mechanical energy to action potentials sent down primary afferent (first order) trigeminal ganglion neurons. The trigeminal ganglion cells form synapses with the trigeminal nuclei of the brainstem, which pass vibrissal signals on via the pons to the contralateral thalamus (Veinante *et al.*, 1999; Pierret *et al.*, 2000), which in turn passes the signals to the whisker regions of the contralateral (relative to the whisker) primary somatosensory cortex (Chmielowska *et al.*, 1989; Bruno and Sakmann, 2006). In addition to the primary somatosensory cortex (S1) there exists in all mammals a secondary somatosensory cortex (Burton, 1986) which, despite what the name suggests, does not follow the primary in a physiological hierarchy, but rather receives direct innervation from the thalamus in parallel to the primary somatosensory cortex (Feldmeyer *et al.*, 2013). S1 provides afferents to the primary motor cortex, which have been shown to possess the anatomical, synaptic, and postsynaptic response characteristics appropriate for strong “driver” inputs (Rocco and Brumberg, 2007; Rocco-Donovan *et al.*, 2011; Petrof *et al.*, 2015), as well as the secondary motor cortex, the secondary somatosensory cortex, cortices for other sensory modalities, the striatum, the superior colliculus, and, for feedback inhibition, the thalamus (Zakiewicz *et al.*, 2013).

The anatomy and physiology of the cortex has been subject to extensive investigation by neuroscientists since the 19th century, with an emerging consensus holding that a basic neocortical circuitry occurs as a repeated anatomical motif across a diverse range of sensory modalities within an organism (a pattern referred to as serial homology) and as a phylogenetically conserved feature across the mammalian clade (Rockel *et al.*, 1980; Douglas and Martin, 2007; Bastos *et al.*, 2012; Harris and Shepherd, 2015).

Neuroanatomists of the early 20th century were the first to note that stained slices of rodent primary somatosensory cortex exhibited arrays of heavily stained, high-density regions running parallel to the brain surface, separated from each other by narrow unstained strips (De Vries, 1912; Rose, 1912; Droogleever Fortuyn, 1914), arrayed similarly to the whiskers on the mystacial pad, leading to the nickname “barrel cortex” being applied to the whisker-

responsive region of the primary somatosensory cortex. These observations were expanded upon by Lorente de Nó (1922), whose work first proposed that the cytoarchitectonic barrels are mirrored in overlapping cortical columns which he divided into a series of six layers, with the layer 4 of his scheme being home to the high-density regions termed “barrels” in the nomenclature put forward by Woolsey and van der Loos (1970). At this point it is worth noting that layers 2 and 3 of Lorente de Nó’s scheme, although distinct, are often examined together as though they were a single layer (known as L2/3) as it is difficult to detect the boundary between the two (Shepherd and Svoboda, 2005; Petersen and Crochet, 2013). Furthermore, layer 5 is customarily divided into two cytoarchitectonically discrete sublayers, L5A and L5B, which receive and distribute signals through independent pathways (Manns *et al.*, 2004). Since then, a consensus has emerged that understanding the distinct morphologies and physiological roles of neuron subtypes within the different layers is critical to understanding the inputs, internal computations, and outputs of the somatosensory cortex (Mountcastle, 1997; de Kock *et al.*, 2007; Douglas and Martin, 2007; Oberlaender *et al.*, 2012; Feldmeyer *et al.*, 2013). The work of Mountcastle and Powell in feline and simian somatosensory cortex in the 1950s (Mountcastle, 1957; Powell and Mountcastle, 1959) and various scientists working in the rat somatosensory cortex in the 1970s (Woolsey and van der Loos, 1970; Welker, 1976; Simons, 1978; Simons and Woolsey, 1979) served to confirm the significance of cortical columns in which functionally cooperative cell-ensembles share key properties, which in the rat barrel cortex include being primarily responsive to stimulation from a single whisker, known as the principal whisker, occupying a location on the mystacial pad analogous to the barrel’s within the barrel field. However, some responsiveness to adjacent whiskers has also been observed, albeit with smaller subthreshold response amplitudes, greater latencies, and smaller post synaptic potentials, with non-principal effects becoming less pronounced with greater distance from the principal whisker (Moore and Nelson, 1998; Zhu and Connors, 1999; Brecht and Sakmann, 2002; Brecht *et al.*, 2003; Manns *et al.*, 2004), a phenomenon also reported in cats (Hellweg *et al.*, 1977). Such topographic organisation of the response fields within the cortex has been documented for cortical regions responding to a range of other sensory modalities,

including audition (Aschauer and Rumpel, 2014), vision (Buckner and Yeo, 2014), and non-vibrissal somatosensation (Dutta *et al.*, 2014). Nonetheless, the organisation of the vibrissal cortex within rats and mice is particularly advanced when compared against other whiskered animals such as opossums, hedgehogs, and the eastern grey squirrel (Killackey, 1973), which reflects the status of rats and mice as vibrissal specialists (Prescott *et al.*, 2011; Grant *et al.*, 2013). Analogous organisations of arrayed zones selectively responsive to individual whiskers has been observed in the ventero-postero-medial nucleus of the thalamus (VPM), with these zones being named “barreloids” (Lu and Lin, 1993; Land *et al.*, 1995; Arnold *et al.*, 2001), and in the trigeminal brainstem nuclei principalis (PrV) and spinal interpolaris (SpVi), where these structures are called “barrelettes” (Erzurumlu *et al.*, 2010).

Action potential responses to vibrissal stimulation in the primary trigeminal afferents (the trigeminal ganglia) of rats and mice have extremely high temporal precision, with one recent study using high sampling rates (100-500 kHz) observing latency jitter on the microsecond range (Bale *et al.*, 2015). Transmission of information from the trigeminal nuclei through to the primary somatosensory cortex occurs via two lemniscal projections, the first of which originates in mono-whisker neurons of the trigeminal nucleus principalis (PrV) and travels through the dorsomedial portion of the VPM (Killackey, 1973; Donaldson *et al.*, 1975; Wise and Jones, 1978; Haidarliu *et al.*, 2008) and terminates mainly in the appropriate barrel column in layer 4, which serves as the main thalamocortical input station in most sensory cortices (Killackey and Leshin, 1975; Creutzfeldt, 1977; Herkenham, 1980; Alloway *et al.*, 1993; Sherman and Guillery, 1996; Diamond, 2013). Projections along this pathway have also been detected terminating in layers 2/3, 5B, and 6, (White, 1978; Henderson and Jacquin, 1995; Lo *et al.*, 1999; Arnold *et al.*, 2001; Constantinople and Bruno, 2013) with one retrograde labelling study suggesting a small percentage terminate in the barrels for adjacent whiskers (Land *et al.*, 1995). The second lemniscal pathway originates in multi-whisker neurons of the PrV, travels through the VPM, and terminates in the septal regions located between cortical barrels (Veinante and Deschênes, 1999; Furuta *et al.*, 2009), from which

these layer 4 septal neurons project into multiple barrels (Wollsey *et al.*, 1975). Additional innervation comes via the paralemniscal projections connecting multi-whisker neurons in the trigeminal nuclei interpolaris (SpVi) through the posterior medial thalamus (Koralek *et al.*, 1988) and on to the barrel cortex (Veinante *et al.*, 2000; Wimmer *et al.*, 2010; Ohno *et al.*, 2011). Transmission of information along this pathway is rapid, with peaks in cortical spike count appearing at a delay corresponding to the summated time for transmission for action potentials across the different relays (Arabzadeh *et al.*, 2006). An additional contributing region not directly in the line of transmission is the reticular thalamic nucleus, a body of GABAergic neurons that receives excitatory input from the thalamus and cortex and provides feedback inhibition onto the VPM (Houser *et al.*, 1980; de Biasi *et al.*, 1986; Shosaku *et al.*, 1989; Pinault, 2004). This is an important inhibitory role within vibrissal signal processing, as interneurons make up less than 5% of the population of the rat VPM itself (Barbaresi *et al.*, 1986; Harris and Hendrickson, 1987; Çavdar *et al.*, 2014), though they have been found in greater abundance in the ventrobasal thalamic complexes of guinea pigs (Spreafico *et al.*, 1994), cats (Madarász *et al.*, 1985; Rinvik *et al.*, 1987) and primates (Smith *et al.*, 1987; Hunt *et al.*, 1991), which has been suggested to indicate greater complexity of local information processing than in the rat thalamus (Arcelli *et al.*, 1997; Sherman, 2004). The reticular thalamic nucleus also receives innervation from thalamic relay cells, with the result of topographically precise feedback inhibition for thalamic relay cells (Lam and Sherman, 2005). The reticular thalamic nucleus receives excitatory innervation from cortical L6, with the effect of disynaptic feedback inhibition of the VPM. Strangely this L6-originating corticothalamic pathway also provides direct innervation to thalamic relay cells, though the dominant effect of L6 stimulation *in vitro* is thalamic inhibition (Lam and Sherman, 2010).

Excitatory Cortical Circuitry

The responses of barrel cortex neurons to whisker stimulation are dependent on the layer and morphology of individual neurons, with several studies providing evidence of

distinct roles for different layers in sensory processing and network dynamics (Beltramo *et al.*, 2013; Reyes-Puerta *et al.*, 2015). de Kock *et al.* (2007) performed single-cell recordings of spiking activity from excitatory neurons in several layers of the barrel cortex with morphological reconstruction. Among their findings were low response likelihoods in L2/3 and the slender-tufted cells of L5A, but more consistent responses in L4, L6, and the thick-tufted cells of L5B. These three consistently responding layers/cell types exhibited similar short latencies, with median values on the order of 14-16 ms. Even in cells that gave a consistent response, though, they never detected an average responsiveness greater than 1 AP per stimulus. This finding is in agreement with the earlier work of Wilent and Contreras (2004) who reported the response amplitudes of 0.45 spikes/stimulus for L2/3, 0.30 spikes/stimulus for L4, and 0.25 spikes/stimulus for L5 and L6, though the variance was such that the interlaminar differences were not statistically significant. These findings in Wilent and Contreras (2004) about the relative responsiveness of the different layers is in disagreement to those reported by de Kock *et al.* (2007), but that is likely due simply to differences in methodology between the two papers. Another consistent finding is that of Sachidhanandam *et al.* (2013) who found that out of 12 excitatory L2/3 cells recorded, only 2 fired robustly in response to PW deflection. Crochet *et al.* (2011) reported a sparse firing of 10% of L2/3 pyramidal neurons to whisker touch in behaving mice. O'Connor *et al.* (2010) found that 10% of barrel cortex neurons in mice fire 50% of spikes during tactile localisation with the highest discriminability in neurons of L4 and L5. Simons and Woolsey (1979) noted that robust deflection responses were much more difficult to obtain in supragranular layers of mouse barrel cortex than in L4, L5, and L6. de Kock *et al.* further reported that thick-tufted L5B cells exhibited the most pronounced surround whisker responses, far greater than that detected in any other group of cells, as well as dominating the evoked output of the cortical column to principal whisker deflection. This led them to suggest that L5 thick-tufted cells may play the key role in directing sensory guided behaviours, a suggestion bolstered by the highly-interconnected nature of these cells, including projections to the thalamus and the motor nuclei of the brainstem (Markram *et al.*, 1997; Jenkinson and Glickstein, 2000; Leergaard *et al.*,

2000; Killackey and Sherman, 2003) as well as the finding that microstimulation of single neurons in the deeper cortical layers can have a behavioural report (Houweling and Brecht, 2008).

Within the barrels themselves individual neurons receive extensive intracortical innervation within and between layers, both excitatory (Feldmeyer, 2012) and inhibitory (Gibson *et al.*, 1999), to the point that thalamocortical synapses onto a typical layer 4 neuron are significantly outnumbered, accounting for only 10-20% of total afferent synapses (White and Rock, 1979; White and Rock, 1980; Benshalom and White, 1986). Nevertheless, thalamocortical axons are able to provide dominant drive to cortical neurons, which some reports attribute to thalamocortical synapses having a higher number of release sites and a higher mean release probability than intracortical axons (Gil *et al.*, 1999), while others attribute thalamic drive to highly synchronous thalamic inputs (Usrey, 2002; Bruno and Sakmann, 2006; Schoonover *et al.*, 2014). Comparisons of the EPSPs evoked in L4 from different inputs have found higher amplitudes from thalamocortical sources than intracortical ones (Lee and Sherman, 2008). The capability of thalamocortical inputs to create the observed features of cortical evoked activity has been found plausible in computational studies using realistic parameters (Bujan *et al.*, 2015). Another class of intracortical connections are trans-columnar arborisations within the barrel cortex (Brecht *et al.*, 2003; Schubert *et al.*, 2003; Manns *et al.*, 2004), which, in conjunction with the paralemniscal projections previously discusses, play a key role in adjacent (non-principal) whisker responses. About 15% of neurons in layer 4 show projections to multiple barrels (Woolsey *et al.*, 1975).

Neuroanatomical studies of the rat somatosensory cortex have found that excitatory neurons account for around 85% of the cortical population in adult rats (Beaulieu, 1993; Micheva and Beaulieu, 1995; Meyer *et al.*, 2011), a proportion consistent with observations made across different species and cortical areas (Somogyi *et al.*, 1998; Douglas and Martin, 2007). This ratio in neurons carries over into synapses, with excitatory synapses in the neocortex known to outnumber inhibitory ones several-fold, with studies in various

neocortical areas finding that around 80-90% of synapses are excitatory (Beaulieu *et al.*, 1992; Douglas and Martin, 2004), creating a powerful recurrent excitation effect (Douglas *et al.*, 1996).

Excitatory neurons can be divided into three main classes defined by axonal projection patterns (Shepherd, 2013; Harris and Shepherd, 2015). The first of these three classes are the intratelencephalic (IT) neurons, which are found in layers 2 through 6 and project axons solely to telencephalon structures such as the neocortex and striatum including the contralateral cortex, which they alone among excitatory cells project to. This category includes the spiny stellate cells of L4, all pyramidal cells of L2/3, L4, and L5A, and a portion of the pyramidal cells in L5B and L6. Pyramidal tract (PT) neurons, not to be confused with pyramidal morphology in general, are found in L5B and project to subcerebral locations and the ipsilateral cortex, striatum, and thalamus. Corticothalamic (CT) neurons are found in L6 and project to the ipsilateral thalamus. In conjunction with the multi-layered inputs of the lemniscal pathways, this diversity of projections demonstrates that cortical circuits exhibit multiple entry and exit points for information transmission (Douglas and Martin, 2004; Feldmeyer *et al.*, 2013; Harris and Shepherd, 2015).

Studies of interlaminar cortical connections in multiple sensory modalities in a variety of species have led to the description of a ‘canonical microcircuit’ consisting of thalamic inputs arriving in L4 cells, which then project to L2/3 neurons, which in turn project to the output neurons in L5 (Douglas *et al.*, 1989; Douglas and Martin, 2004; Douglas and Martin, 2007; Hooks *et al.*, 2011; Bastos *et al.*, 2012; Feldmeyer *et al.*, 2013), an example of what anatomists call ‘serial homology’, or a similarity of organisation in different structures within an organism (Harris and Shepherd, 2015). It should be stressed, however, that this model is a simplification, as L5 neurons receive direct paralemniscal inputs (Oberlaender *et al.*, 2011) and L5 principal whisker responses are preserved even after lesion of L2/3 neurons (Huang *et al.*, 1998).

In L4 of the barrel cortex, spiny stellate cells account for 80% of the neuronal population (Lübke *et al.*, 2000; Lefort *et al.*, 2009) and are the major cell type receiving thalamic inputs (Killackey and Leshin, 1975; Herkenham, 1980; Lübke *et al.*, 2000). Spiny stellate cells are known to form extensive connections within their barrel, including reciprocal connections of each spiny stellate neuron with an estimated 20-30% of the others (Feldmeyer *et al.*, 1999; Petersen and Sakmann, 2000) such that L4 comes to account for ~30% of synaptic boutons from spiny stellate cells (Lübke *et al.*, 2000). Trans-barrel excitatory projections between L4 spiny stellates, however, are rare (Petersen and Sakmann, 2000; Schubert *et al.*, 2003), as reflected in the absence of direct activity propagation between barrels (Petersen and Sakmann, 2001; Laaris and Keller, 2002) and the observation that neurons of L4 show no plasticity of receptive fields after whisker trimming (Diamond *et al.*, 1994). L4 spiny stellates' connections also include projections to L2/3 pyramidal cells (Feldmeyer *et al.*, 2002; Thomson *et al.*, 2002; Hooks *et al.*, 2011), L2/3 interneurons (Thomson *et al.*, 2002; Helmstaedter *et al.*, 2008), and L5A pyramidal cells (Thomson *et al.*, 2002; Feldmeyer *et al.*, 2005), though L2/3 is the major non-granular projection destination (Lübke *et al.*, 2003), accounting for ~45% of synaptic boutons from L4 spiny stellates (Lübke *et al.*, 2000). The minority L4 pyramidal cells, on the other hand, show inputs from nongranular layers within their columns as well as from neighbouring barrels (Lübke *et al.*, 2000; Schubert *et al.*, 2003), and are thought to receive some direct thalamic input themselves (Miquelajauregui *et al.*, 2015). Similar to spiny stellate cells, L2/3 and L4 account for most of their projections, with ~45% and ~25% of synaptic boutons found in L2/3 and L4, respectively, with some trans-columnar axonal projections observed in L2/3 (Lübke *et al.*, 2000).

In addition to inputs from L4, pyramidal cells in L3 have been shown to receive some excitation from the thalamus VPM, with probability of contact decreasing with distance from the L3-L4 laminar border (White and Hersch, 1981; Johnson and Alloway, 1996). L2/3 pyramidal neurons project densely to L5 pyramidal neurons (Thomson *et al.*, 2002; Hooks *et al.*, 2011), providing excitatory input to L5 apical dendrites that have been shown to reach

L2/3 (White and Peters, 1993). L2/3 pyramidal neurons have been shown to directly excite L2/3 interneurons (Rozov *et al.*, 2001; Thomson *et al.*, 2002; Kaiser *et al.*, 2004), with pyramidal-interneuron connections being much more numerous than inter-pyramidal connections (Holmgren *et al.*, 2003). L2/3 pyramidal neurons vertically project to all layers of the column, and though their dendrites are restricted to within the column they also have trans-columnar axonal projections branching horizontally in L2/3 and L5 (Gottlieb and Keller, 1997; Lübke *et al.*, 2003), a connection pattern reflected in trans-columnar excitation being primarily associated with L2/3 and L5 (Petersen and Sakmann, 2001). L2/3 pyramidal cells provide excitatory input to L4 interneurons, thus providing negative feedback to L4 excitatory neurons (Thomson *et al.*, 2002). They are also known to project to other brain regions, such as the primary motor cortex (Mao *et al.*, 2011).

The importance of L2/3-L2/3 interconnections was suggested in a computational modelling study of L2/3 excitability based on anatomical findings about L2/3-L2/3 and L4-L2/3 connections that predicted a post-deflection firing probability of 0.35 for any given L2/3 neuron (Sarid *et al.*, 2015), reflective of empirical findings (Simons and Woolsey, 1979; Wilent and Contreras, 2004; de Kock *et al.*, 2007).

Pyramidal neurons of L5 are known to project apical dendrites into layer 2/3 where they encounter the shorter apical dendrites of the more superficial pyramidal cells (White and Peters, 1993). Additional arborisations from the main apical dendrite commonly reach L1 (Chagnac-Amitai *et al.*, 1990). L5 pyramidal neurons receive some direct input from the thalamus (Gil and Amitai, 1996), with most of their thalamocortical synapses occurring on basal dendrites in L5 but a considerable number occurring on the apical dendrite as it passes through L4 (Rah *et al.*, 2013). In L5A, this thalamic input is from the paralemniscal pathway (Lu and Lin, 1993), whereas in L5B it arrives from the lemniscal pathway (Chmielowska *et al.*, 1989; Lu and Lin, 1993). The pyramidal neurons in L5A have a high degree of interconnectivity, with Lefort *et al.* (2009) finding that two such neurons have a 20% chance of being synaptically connected, though the connectivity in L5B is less than half that figure.

The neurons of L5B provide excitatory input to L6 (Lefort *et al.*, 2009) as well as other brain regions, such as the primary motor cortex (Mao *et al.*, 2011).

The excitatory pyramidal cells of layer 6 have a very low degree of inter-connectivity (Lefort *et al.*, 2009). Intracortical inputs to L6 have been detected from L4 and L5B, but L6 outputs to other layers are fairly weak (Lefort *et al.*, 2009; Hooks *et al.*, 2011). Excitatory synapses from L6 to L4 are known to exist, but produce EPSPs of low amplitude compared to thalamocortical inputs to the same L4 neurons (Lee and Sherman, 2008; Lee and Sherman, 2009) and are quickly followed by strong IPSPs, suggesting that L6 neurons are recruiting interneurons (Schubert *et al.*, 2003). A recent study found evidence of L6 excitatory input to L5A, including optogenetic stimulation of L6 causing action potential responses in L5A pyramidal neurons, though interneurons were recruited more readily in both L5A and L4 (Kim *et al.*, 2014). Such effects suggest a role in controlling cortical output, as L5A is considered the main output layer (Feldmeyer, 2012). L6 neurons with horizontal axons have been documented, suggesting a role in communication with adjacent barrels (Gottlieb and Keller, 1997; Marx and Feldmeyer, 2013). L6 excitatory neurons also provide feedback inhibition to the thalamus by way of their projections to the thalamic nucleus reticularis (Lam and Sherman, 2010). Additional projection targets for L6 excitatory neurons include S2, the motor cortex, and the corpus callosum (Zhang and Deschênes, 1997).

In addition to layer and morphology, neurons of the barrel cortex may be subdivided based on functional properties, such as spike waveform and frequency. The two major subclasses in this case are fast-spiking units (FSUs) and regular-spiking units (RSUs), with the latter accounting for about 85% of cortical neurons (Simons and Woolsey, 1979; Bruno and Simons, 2002). FSUs are known for the short durations of both the depolarisation and hyperpolarisation of their action potentials (given ranges of 130-179 μ s and 185-567 μ s, respectively, in Bruno and Simons, 2002), their high spontaneous and evoked firing rates, broad receptive fields, and low directional selectivity. RSU have longer durations of both their depolarisation and hyperpolarisation periods (given ranges of 195-418 μ s and 422-837 μ s,

respectively, in Bruno and Simons, 2002), as well as lower spontaneous and evoked firing rates, narrow receptive fields (often comprising a single whisker), and higher directional selectivity (Mountcastle *et al.*, 1969; Simons, 1978; Simons and Carvell, 1989; Armstrong-James *et al.*, 1993; Kyriazi *et al.*, 1994; Bruno and Simons, 2002). It is widely agreed that the majority of FSUs comprise a significant subclass of inhibitory neurons (Kawaguchi and Kubota, 1993; Gibson *et al.*, 1999; Rudy *et al.*, 1999; Porter *et al.*, 2001), though it should be stressed that in some cases fast-spike action potentials have been recorded from cells that, upon labelling and histological recovery, were found to have the morphology of pyramidal excitatory cells (Dykes *et al.*, 1988; Gray and McCormick, 1996). RSUs are regarded as mainly a population of excitatory neurons (Kyriazi *et al.*, 1996; Bruno and Simons, 2002), though such spikes have also been documented from GABAergic neurons in some cases (Kawaguchi and Kubota, 1993; Gibson *et al.*, 1999).

Inhibitory Cortical Circuitry

Excitation and inhibition go hand in hand, with excitatory and inhibitory inputs to cortical cells being highly synchronised during both vibrissal stimulation (Wilent and Contreras, 2005; Okun and Lampl, 2008) and spontaneous activity (Shu *et al.*, 2003; Haider *et al.*, 2006). The term “interneuron” itself derives from the fact that such inhibitory neurons generally provide dense inhibitory input locally, connecting to a greater percentage of local excitatory neurons than excitatory neurons themselves do (Holmgren *et al.*, 2003; Fino and Yuste, 2011; Avermann *et al.*, 2012; Caputi *et al.*, 2013; Karnani *et al.*, 2014), although there are documented examples of GABAergic neurons forming long-range projections between brain structures with distinct functions (Caputi *et al.*, 2013). Paired recordings in thalamocortical slices have shown that L4 barrel cortex fast-spiking interneurons form extensive arborisations within their barrels and provide inhibitory connections of greater synaptic conductance than local excitatory connections (Sun *et al.*, 2006). Thalamic afferents innervate cortical interneurons via some of the most powerful synapses in the cortex, with a

high number of neurotransmitter release sites and a high probability of release (Sun *et al.*, 2006; Cruikshank *et al.*, 2007; Bagnall *et al.*, 2011). Past studies have produced evidence that inhibitory cortical neurons play a key role in creating the stimulus property selectivity of excitatory neurons (Isaacson and Scanziani, 2011; Merchant *et al.*, 2012). Pharmacologically, it has been reported that application of GABA_A antagonist bicuculline methiodide reduces orientation selectivity in the visual cortex (Nelson, 1991) and broadens receptive fields in feline somatosensory cortex (Hicks and Dykes, 1983) and that the application of GABA_A receptor antagonists causes disinhibition of adjacent whisker responses in barrel cortex (Foeller *et al.*, 2005). It has also been reported that direction-selectivity in the barrel cortex arises despite broadly tuned excitatory and inhibitory input by shifts in the temporal relation of the two (Wilent and Contreras, 2005). In a study involving paired simultaneous recordings of neurons from corresponding thalamic barreloids and cortical barrels in rats, Bruno and Simons (2002) found that FSUs were twice as likely as RSUs to exhibit evidence of excitatory input from their paired thalamic neurons and that thalamic-FSU connections showed greater connection efficacy than thalamic-RSU ones. Similar findings were reached in studies in rabbit barrel cortex (Swadlow, 1995; Swadlow and Gusev, 2002). This suggests more effective thalamic drive for inhibitory cortical neurons rather than their excitatory counterparts, underscoring a critical role for interneurons in response tuning of excitatory cells. Analogous response selectivity roles have also been proposed in other sensory cortices, such as the auditory cortex (Razak and Fuzessery, 2009, 2010). Interneurons of barrel cortex L4 serve a key role as the mechanism of feedforward inhibition from the thalamus, with both whole animal and *in vitro* studies finding that these neurons are subject to reliable and temporally precise activation by thalamocortical inputs. These excitatory inputs enable the interneurons to tune L4 excitatory behaviour by suppressing all excitatory neurons except those subject to the strongest excitatory thalamic inputs (Swadlow, 2002, 2003; Sun *et al.*, 2006; Kwegyir-Afful *et al.*, 2013). A feedforward inhibition role for interneurons may also apply to intracortical circuits, as suggested by the finding that the unitary EPSPs L4 spiny stellates elicit in L2/3 interneurons have an average amplitude double those elicited by L2/3

pyramidal neurons (Helmstaedter *et al.*, 2008) and the observation of L2/3 pyramidal cells exciting interneurons in L5 (Kapfer *et al.*, 2007). Barrel cortex interneurons also provide inhibition of adjacent barrels by way of trans-columnar GABAergic projections (Kätzel *et al.*, 2011). The likelihood of firing in response to thalamocortical stimulation is much higher in inhibitory interneurons than in excitatory cells (Porter *et al.*, 2001), which is consistent the *in vivo* observation that inhibitory neurons can be made to reliably fire at lower vibrissal deflection intensities than their excitatory peers (Swadlow, 2002, 2003). Interneurons also provide powerful recurrent inhibition, with even single pyramidal cells in L2/3 (Kapfer *et al.*, 2007) and L5 (Silberberg and Markram, 2007) able to recruit intralaminar interneurons. Further evidence for recurrent inhibition arises from a study finding that inhibitory inputs to cortical neurons largely derive from interneurons of the same layer (Kätzel *et al.*, 2011). It has been proposed that interneurons play a key role in the functional maturation of the cortex as a whole through their effects on overall wiring, plasticity, and network activity (McBain and Fisahn, 2001; Hensch and Fagiolini, 2005; Le Magueresse and Monyer, 2013; King *et al.*, 2013).

Inhibitory neurons in the cortex display considerable diversity in terms of morphology, activity, and neurochemistry, with considerable evidence and general consensus that this reflects distinct functional roles and synaptic connection properties (Keller and White, 1987; Dantzker and Callaway, 2000; Porter *et al.*, 2001; Ascoli *et al.*, 2008; Burkhalter, 2008; Xu and Callaway, 2009; Sultan *et al.*, 2013; Kim *et al.*, 2014; Kubota, 2014; Petersen, 2014; Chen *et al.*, 2015; Sessolo *et al.*, 2015). While it is generally agreed that inhibitory projections are much likely to arise from non-pyramidal neurons than pyramidal ones (Kawaguchi and Kubota, 1997; DeFelipe, 2002; DeFelipe *et al.*, 2013), some interneurons do express morphologies resembling pyramidal neurons (Uematsu *et al.*, 2007). Several morphological subtypes have been documented for non-pyramidal cortical interneurons (Markram *et al.*, 2004; Jiang *et al.*, 2013; Kubota *et al.*, 2014), including basket cells (Zhang and Deschênes, 1997), Martinotti cells (Wang *et al.*, 2004; Silberberg and Markram, 2007), double bouquet

cells (Ramos-Moreno and Clascá, 2014), single bouquet cells (Lee *et al.*, 2014), neurogliaform cells (Xu and Callaway, 2009; Marco García *et al.*, 2015), bipolar cells (Rozov *et al.*, 2001), bitufted cells (Kaiser *et al.*, 2001; Kaiser *et al.*, 2004), and chandelier cells (Zhu *et al.*, 2004). Efforts at classifying cortical interneurons neurochemically have led to the finding that nearly all can be put into one of the three grouping based on whether they express the Ca²⁺-binding protein parvalbumin (PV, ~40% of population), the protein somatostatin (SST or SOM, ~30%), or the ionotropic serotonin receptor 5HT3a (~30%), the last of which includes as a subgroup all interneurons expressing vasoactive intestinal polypeptide (VIP) (Rudy *et al.*, 2011). A rich diversity of these neurochemical classes can be identified not only within the barrel cortex overall but also within distinct barrel cortex layers (Karagiannis *et al.*, 2009; Perrenoud *et al.*, 2013).

Evidence for functional correlates to interneuron morphologies have been suggested by a study finding that the responses of L2/3 interneurons to repetitive L4 spiny stellate stimulation displayed variable adaptation properties according to their morphologies (Helmstaedter *et al.*, 2008; for further details, please see the “Adaptation” section). One further example can be found in the case of chandelier interneurons of L2/3, which are unusual in that they rarely fire spontaneously or in response to whisker deflections, and have instead been proposed to function as powerful suppressive cells in case of high overall cortical excitation (Zhu *et al.*, 2004). Another example can be found in the interneurons of L1, where it has been shown that different morphology classes correlate with different receptive field sizes (Zhu and Zhu, 2004). Neurochemical classifications of cortical interneurons have also been shown to have functional correlations, such as different degrees of connectivity with local excitatory cells (Beierlein *et al.*, 2003; Hofer *et al.*, 2011; Pala and Peteresen, 2015) and L6 pyramidal cells more readily recruiting parvalbumin-expressing neurons than somatostatin-expressing interneurons (Kim *et al.*, 2014).

Diversity in the behaviour of interneurons can also be observed when comparing fast-spiking and non fast-spiking interneurons. A study of intracortical connections between L2/3

pyramidal cells and L2/3 interneurons found that FSU interneurons were more reliably stimulated by the excitatory neurons that were non-FSU interneurons (Mateo *et al.*, 2011). While L4 spiny stellate and star pyramidal cells produce EPSPs of similar amplitude in either FS or non-FS interneurons, it has been observed that FS interneurons produce IPSCs of greater amplitude than non-FS interneurons in L4 spiny stellate and pyramidal excitatory cells (Sun *et al.*, 2006). Conversely, in L2/3 it has been observed that pyramidal cells produce higher amplitude EPSPs in FS interneurons than non-FS ones, though in this layer FS and non-FS interneurons evoked IPSPs of similar amplitude in pyramidal cells (Avermann *et al.*, 2012).

Adaptation

Introduction to Adaptation

Neuronal responses to whisker deflection are dynamic, with response functions shifting in response to prior stimuli, a phenomenon known as adaptation (Barlow and Földiák, 1988). First described by Adrian (1928) in cutaneous receptors, adaptation is commonly observed in neurons from all sensory systems (Khatri and Simons, 2007; Wark *et al.*, 2007), with literature reports from visual (Blakemore and Campbell, 1969; Movshon and Lennie, 1979; Dragoi *et al.*, 2000), olfactory (Wilson, 1998), and auditory neurons (Ulanovsky *et al.*, 2004; Dean *et al.*, 2005; Behrens *et al.*, 2009), as well as whisker-responsive neurons in other species, such as cats (Hellweg *et al.*, 1977). Adaptation has been documented in human somatosensation, such as shifting of stimulus detection thresholds (Laskin and Spencer, 1979; Gescheider *et al.*, 1995; Höffken *et al.*, 2013; Custead *et al.*, 2015) and changes in ability to discriminate between two stimuli of different intensities (Goble and Hollins, 1993; Tannan *et al.*, 2007) in response to a conditioning stimulus. Adaptation serves an important role in achieving efficient coding of sensory stimuli (Fairhall *et al.*, 2001; Wark *et al.*, 2007). From a medical perspective, it has been proposed that sensory adaptation plays a critical role in recovery of sensory and motor function in stroke patients (Staines *et al.*, 2002) and that impairments of adaptation may contribute to the symptoms of some neurological disorders such as autism (Pellicano *et al.*, 2007; Tannan *et al.*, 2008; Cellot and Cherubini, 2014;

Daluwatte *et al.*, 2015) and schizophrenia (O'Donnell, 2011). Understanding and reliably replicating neuronal adaptation behaviours may also prove critical in the development of brain-machine interface technologies (Musall *et al.*, 2014). It has been proposed that the underlying mechanisms of short-term adaptation may also play a role in adjustments of neocortical anatomical connections in response sensory experience and that the dynamics of short-term adaptation itself may be altered by long-term sensory experiences (Finnerty *et al.*, 1999).

The earliest explorations of adaptation behaviours in somatosensory pathways *in vivo* are those of Adrian and Zotterman (1926), who recorded afferent impulses of the plantar digital nerves of cats while applying pressure to the toes of anaesthetised cats. They found that application of pressure resulted in increased impulse frequency that peaked during the increase of pressure and then declined rapidly when the pressure was maintained at a constant level, with maximum frequency value being correlated more with the rate of pressure increase than on the final pressure amplitude. In one stage of their experiments they released pressure from the cat's toe and then renewed it after a short interval, thus conducting the earliest adaptation experiments based on the paired-pulse paradigm, and found that full recovery from a previous state of adaptation could be obtained after allowing 2 seconds of rest for the cat's toe.

Adaptation in the Whisker Somatosensory Pathway

Within the rat *whisker-barrel* pathway, adaptation has been observed at all levels, including trigeminal ganglion cells (Gibson and Welker, 1983; Lichtenstein *et al.*, 1990; Fraser *et al.*, 2006; Jones *et al.*, 2004), trigeminal nuclei (Minnery and Simons, 2003), the thalamus (Waite, 1973; Fanselow and Nicolelis, 1999; Cohen-Kashi Malina *et al.*, 2013), the barrel cortex (Fanselow and Nicolelis, 1999; Garcia-Lazaro *et al.*, 2007; Maravall *et al.*, 2007; Adibi *et al.*, 2013a; Cohen-Kashi Malina *et al.*, 2013), and the secondary somatosensory cortex (Kwegyir-Afful and Keller, 2004). Such multi-level adaptation parallels what has been documented for other sensory systems, such as audition (Malmierca *et al.*, 2014) and vision

Table 1: Adaptation Behaviours of Specific Inter-Neuronal Connections to Repetitive Stimuli

Pre-Synaptic Neuron	Post-Synaptic Neuron	Adaptation Behaviour in Post-Synaptic Neuron	Reference
Thalamic	L4 spiny neurons	Depression	Gil <i>et al.</i> , 1999; Gabernet <i>et al.</i> , 2005; Viaene <i>et al.</i> , 2011
		Depression predominant, but some cases of facilitation	Díaz-Quesada <i>et al.</i> , 2014
	L4 PV-expressing FS interneurons	Depression	Tan <i>et al.</i> , 2008
	L5 PV-expressing FS interneurons		
	L3 SOM-expressing interneurons	Facilitation	Viaene <i>et al.</i> , 2011
	L2/3 pyramidal neurons		
L4 spiny stellate	L4 spiny stellate	Depression	Petersen, 2002
		Depression or possibly weak facilitation	Gil <i>et al.</i> , 1999
	L2/3 pyramidal	Depression	Finnerty <i>et al.</i> , 1999; Feldmeyer <i>et al.</i> , 2002; Bender <i>et al.</i> , 2006
	L5A pyramidal		Feldmeyer <i>et al.</i> , 2005
	L2/3 bipolar interneurons	Facilitation	Helmstaedter <i>et al.</i> , 2008
	L2/3 “large basket cell” interneurons	Depression	

	L2/3 neuragliaform interneurons		
L4 FS interneurons	L4 excitatory neurons	Depression	Gabernet <i>et al.</i> , 2005
L2/3 pyramidal	L2/3 pyramidal	Depression	Finnerty <i>et al.</i> , 1999; Holmgren <i>et al.</i> , 2003; Feldmeyer, <i>et al.</i> , 2006; Kapfer <i>et al.</i> , 2007
		Facilitation	Gil <i>et al.</i> , 1997; Holmgren <i>et al.</i> , 2003
	L2/3 VIP-expressing bipolar interneurons	Depression (absent in uIPSCs in reverse)	Rozov <i>et al.</i> , 2001
	L2/3 SOM-expressing bitufted/multipolar interneurons	Facilitation (depression of uIPSCs in reverse)	Reyes <i>et al.</i> , 1998; Kaiser <i>et al.</i> , 2004; Kapfer <i>et al.</i> , 2007; Fanselow <i>et al.</i> , 2008; Pala and Petersen, 2015
	L2/3 PV-expressing FS interneurons	Depression	Reyes <i>et al.</i> , 1998; Holmgren <i>et al.</i> , 2003; Kapfer <i>et al.</i> , 2007 (but not observed in Pala and Petersen, 2015)
L5 pyramidal	L5 pyramidal	Facilitation	Markram and Tsodyks, 1996
L5 interneuron	L5 pyramidal	Depression	Xiang <i>et al.</i> , 2002

Table 1: The results described in this table involved repetitive electrical stimulation of the pre-synaptic neuron and recording of responses in the post-synaptic neuron. Depression and facilitation in the post-synaptic neuron refer to a decrease or increase, respectively, of post-synaptic neuron responses to post-initial stimuli in a train of repetitive stimuli.

(Dhruv and Carandini, 2014). Adaptation behaviours have been observed in a variety of intracortical connections, as documented in Table 1.

Adaptation to Sustained Stimuli

The nature and degree of adaptation are known to change along the lemniscal vibrissal pathway, with neurons in the trigeminal ganglia and nuclei primarily displaying “tonic” responses, in which sustained stimulation results in plateau (steady-state) firing rates which, while lower than that initially evoked, are still elevated above baseline (Minnery and Simons, 2003). Exposed to stimulus intensities sufficient to cause adaptation in the brainstem, neurons of the thalamus (Hartings and Simons, 2000) and cortex (Simons and Carvell, 1989) more commonly display “phasic” responses in which steady-state firing rates do not exceed spontaneous responses. Another way of describing these differences is considering adaptation to a sustained stimulus, which a neuron can respond to either with a non-zero steady state firing rate (termed “slowly adapting”) or with a steady-state characterised by total cessation of the firing response (termed “rapidly adapting”) (Petersen *et al.*, 2009).

Adaptation to Repetitive Stimuli

Another important mode for exploring adaptation is to consider how neurons respond to each stimulus presented in a train of repeated stimuli given at consistent intervals (Petersen *et al.*, 2009). This form of adaptation is the principal focus of this document. Studies comparing adaptation to whisker deflection trains of comparable intensities in the various stations along the afferent vibrissal signal pathway from brainstem to cortex have found that steady-state adaptation became deeper in higher-level brain regions further along both the lemniscal and paralemniscal pathways, with cases documented of brainstem stations not exhibiting any depression to trains causing substantial depression of the cortex (Ahissar *et al.*, 2000; Ganmor *et al.*, 2010; Martin-Cortecero and Nuñez, 2014). It has been shown that adaptation in cortical neurons is more substantial than in thalamic cells through studies of firing rates (Khatri *et al.*, 2004) and sub-threshold conductances (Heiss *et al.*, 2008). Chung *et al.*, (2002) reported slower recovery from adaptation in the barrel cortex than in the VPM

that matched the deeper adaptation in cortex, though it should be noted that they were comparing intracellularly recorded EPSPs in the cortex to extracellularly recorded firing in the VPM. This magnification of adaptation effects as signals are transmitted through a processing hierarchy is mirrored by findings of magnetoencephalography studies in humans comparing adaptation as finger stimulation signals travel from the primary somatosensory cortex to the posterior parietal cortex (Popescu *et al.*, 2013; Venkatesan *et al.*, 2014).

Within the barrel cortex, it has been shown that increasing the frequency of stimuli in a train of otherwise identical whisker deflections causes the depth of adaptation in steady state as measured by adaptation index (the adapted spike rate response to a deflection normalised by the pre-adaptation spike rate response to such a deflection) to increase as well (Khatri *et al.*, 2004; Musall *et al.*, 2014). An intriguing factor in the frequency-dependence of adaptation to repetitive stimuli is that some neurons exhibit a rebound excitation period after suppression, which can result in facilitative adaptation if the frequency is set to coincide with this rebound excitation period (Stanley and Webber, 2004). It has also been shown that the time-course and depth of adaptation to repetitive stimulation trains can depend on the direction of whisker stimulation, even within the activity of a single neuron (Webber and Stanley, 2006). From a spatiotemporal perspective, it has been observed that a neuron's timecourse for adaptation to repetitive stimuli differs when repetitive stimuli are applied to the principal whisker compared to when repetitive stimuli are applied to adjacent whiskers (Bolori and Stanley, 2006). An *in vitro* pair-recording study of L5 cortical neuron pairs in rats found that prolonged presynaptic stimulation resulted in depression of post-synaptic currents, with both initial and steady-state depression magnitudes being directly correlated with stimulation frequency (Galarreta and Hestrin, 1998). Notably, the depression effects on excitatory synapses were greater than those on inhibitory ones at comparable frequencies, suggesting that inhibitory effects in the cortex will peak at more intense stimulus levels than excitatory effects.

Although adaptation is most commonly thought of as a reduction in neuronal response magnitudes to stimuli that are recently preceded by similar stimuli, it is important to note that

repeated stimuli have been observed to sometimes increase neuronal response magnitudes, a phenomenon known as facilitation. This process has been observed in the barrel cortex (Derdikman *et al.*, 2006; Cohen-Kashi Malina *et al.*, 2013) as well as other sensory systems, such as the visual cortex of macaques (Wissig and Kohn, 2012), and regions of inferior colliculus with a role in auditory processing in bats (Grinnell and Hagiwara, 1972; Möller, 1978). The possibility of both suppressive and facilitative effects from adaptation points to an intricate interplay of changes in the excitatory and inhibitory inputs to neurons. A model for understanding this balance of excitation and inhibition is laid out in a recent review by Solomon and Kohn (2014), who point out, based on work in visual cortex, that the receptive fields of sensory processing neurons are composed of both a classical receptive field (CRF) that directly elicits action potentials from the neuron and a normalisation field that has a divisive effect on CRF output and thus serves an inhibitory role. It has been shown that adaptation can weaken both the CRF, resulting in weakened excitation, and the normalisation field, which has a disinhibitory effect on the neurons it projects to (Webb *et al.*, 2005; Wissig and Kohn, 2012). Additionally, time-courses of adaptation and recovery thereof often vary between the CRF and normalisation fields (Bair *et al.*, 2003; Smith *et al.*, 2006; Henry *et al.*, 2013), with the result that the predominant effect of adaptation on a single neuron may range from strong suppression to strong facilitation based on the dynamics of each field's inputs at a given post-adaptor time point.

In a study of touch-dependent adaptation in anaesthetised rats, laminar differences in adaptation behaviours were observed in the somatosensory cortex (Derdikman *et al.*, 2006). The authors performed extracellular neuron recordings while applying electrically induced artificial whisking either in air or against an object. They observed depression of neuronal responses in L2/3 in both free whisking and touch conditions with greater depression in free whisking, facilitation in L5A in both free whisking and touch, and facilitation in L4 only under the touch condition. The authors attributed these results to the different inputs of the layers, so that the differences in responses in L4 and L5A are due to the segregation of various active

touch signals between different parallel afferent pathways: whisking signals by paralemniscal, contact signals by extralemniscal, and combined whisking and touch signals by lemniscal pathways (Yu *et al.*, 2006). These results provide a demonstration of the way in which different adaptation behaviours can correlate to different functional behaviours of neurons. Also of note is that in L4 and L5A steady state action potential responses across the population were facilitated, whereas in studies using passive deflections facilitation of spike counts was observed either only at low frequencies (Garabedian *et al.*, 2003) or only in L4 spiny stellate cells (Brecht and Sakmann, 2002).

Mechanisms of Adaptation to Repetitive Stimuli

A number of papers have been published that explore the dynamics and possible mechanisms of adaptation to repetitive stimuli in the whisker-responsive pathway. A study by Chung *et al.* (2002) found that whisker-induced adaptation in the barrel cortex is not accompanied by significant changes in intrinsic membrane properties (which argues against postsynaptic factors accounting for adaptation) nor much depression of intracortical synapses, but it is correlated with depression of thalamocortical synapses. The negligible adaptation in barrel cortex neurons directly stimulated by optogenetic stimulation trains (Musall *et al.*, 2014; Pala and Petersen, 2015) provides further evidence against internal cellular mechanisms for adaptation, as does the fact that FSUs display deeper adaptive attenuation to whisker deflection trains than cortex-projecting thalamic barreloid cells do (Khatri *et al.*, 2004) despite showing no adaptation to direct stimulation by square pulses of current (Connors and Gutnick, 1990; Agmon and Connors, 1992). Further evidence against internal cellular mechanisms arises from the fact that although EPSPs from thalamocortical stimulation of L3 pyramidal cells show paired-pulse depression, no such depression is observed if the thalamocortical stimulation is followed by an EPSP from intracortical stimulation (Gil *et al.*, 1997).

At present the leading mechanism proposal is short-term synaptic dynamics (Chung *et al.*, 2002; Ganmor *et al.*, 2010; Rosenbaum *et al.*, 2012; Díaz-Quesada *et al.*, 2014), a depletion of synaptic transmission resources (Fioravante and Regehr, 2011) that has been

documented in thalamic inputs to cortex (Gil *et al.*, 1997; Lee and Sherman, 2008; Díaz-Quesada *et al.*, 2014; Kloc and Maffei, 2014; Schoonover *et al.*, 2014) as well as intracortical connections (Sun and Zhang, 2011; Ma *et al.*, 2012; Pala and Petersen, 2015). Short-term plasticity of the voltage-gated Ca^{2+} channel dependent synapses common in the central nervous system has been shown to manifest itself as both depression and facilitation of synaptic strength, with timescales on the order of hundreds of milliseconds to seconds (Catterall *et al.*, 2013).

An *in vitro* study of short-term plasticity of thalamocortical synapses in mice found a rich diversity of adaptation ratios (Díaz-Quesada *et al.*, 2014), which supports the hypothesis of synapses being the generation site for cortical adaptation as it would help explain how adaptation can take the form of suppression or facilitation of an individual neuron's stimulus responses. It has also been observed that intracortical excitatory synapses in barrel cortex L4 display high degrees of synaptic plasticity (Rollenhagen *et al.*, 2014). Furthermore, an *in vivo* study tested the rival hypothesis of cortical adaptation arising from feedback inhibition by exploring cortical adaptation to whisker stimulus train in the absence or presence of GABA_A receptor agonist muscimol in Layers 2/3 or 5/6 of the barrel cortex. This study found no effect on neuronal adaptation from muscimol application, providing further support for the synaptic origin hypothesis (Martin-Cortecero and Nuñez, 2014). The same study also cast doubt on subcortical adaptation being due to corticofugal projections from the cortex by demonstrating that cooling of the cortex did not reduce subcortical adaptation. The hypothesis of adaptation being due to feed-forward inhibition from thalamic inputs has been disputed based on the observation that paired-pulse depression of L4 thalamocortical synapses is still observed in the presence of GABA_A receptor antagonists (Lee and Sherman, 2008). These findings mirror those from earlier studies of feline and rodent visual cortex that found no effect on paired-pulse suppression from application of GABA_A antagonist bicuculline methiodide (Nelson, 1991; Froemke and Dan, 2002). The view of thalamocortical synapses as the site of origin of cortical adaptation is in line with evidence suggesting that build-up of depression at

trigeminothalamic synapses serves as the origin for adaptation to deflection trains in the VPM (Castro-Alamancos, 2002; Deschênes *et al.*, 2003). A synaptic basis for adaptation effects can account for the target-specificity in paired-pulse paradigm responses in thalamocortical slices, such as in the case of excitatory inputs from L2/3 pyramidal cells causing paired-pulse depression or paired-pulse facilitation in different interneuron classes (Reyes *et al.*, 1998; Koester and Johnston, 2005; Lu *et al.*, 2007) and the fact that excitatory inputs from L5 pyramidal neurons show depression in the case of projections onto other L5 pyramidal cells and facilitation in the case of projections onto L5 interneurons (Markram *et al.*, 1998).

One interesting observation that lends further support is that cortical adaptation following the stimulation of a barrel's principal whisker does not transfer to responses to stimulation of an adjacent whisker nor vice versa (Katz *et al.*, 2006; though see Boloori and Stanley, 2006), which is in agreement with a synaptic basis for adaptation due to excitation from adjacent whiskers arriving at barrel cortex neuron from a different set of synapses than excitation from the principal whisker. A similar observation in visual cortex, where neurons commonly have a preferred orientation, is that adaptation to a grating of orthogonal orientation does not have an adaptation effect as strong as that from prior exposure to the preferred adaptation (Carandini *et al.*, 1998).

Synaptic depression of thalamocortical synapses has also been observed in the case of primary visual cortex in cats during delivery of electrical stimulation to the thalamus, with the interesting observation that post-synaptic potential amplitude reductions were greater in cortical neurons that were indirectly excited by thalamus than those directly excited by thalamus, which may be due to compounding of depression effects at corticocortical synapses (Boudreau and Ferster, 2005). An *in silico* exploration of the ability of a synaptic depression model to adequately explain observed responses of cortical neurons to thalamic input was also performed using cat primary visual cortex, with a single layer 4 spiny stellate cell given inputs from a synapse population reflecting empirically observed proportional contributions from various sources (Banitt *et al.*, 2007). This model replicated biologically observed light

stimulus orientation tuning to the satisfaction of the authors, with the caveat that a model of one cortical cell cannot properly incorporate recurrent activity within the cortex. Short-term synaptic depression has also been advanced as a major explanatory factor in auditory processing (David *et al.*, 2009; Yang and Xu-Friedman, 2015). Short-term synaptic dynamics have been shown to impose a frequency-dependent filter on information transfer across the synapse, with stochastic rates of recovery from vesicle depletion in the presynaptic neurons' axon terminals (Rosenbaum *et al.*, 2012).

Sole reliance on the synaptic depression hypothesis is challenged, however, by recordings from cortical neurons which examined the effect on adaptation ratios of increased intensity of whisker stimulation (Ganmor *et al.*, 2010). Based on the synaptic depression model, Ganmor *et al.* predicted that when whiskers were presented with whisker deflection trains of two different amplitudes, the higher amplitude train would cause greater depression of the thalamocortical synapses and hence deeper adaptation would be seen in responses to deflections later in the train. In contrast, they found the opposite to be true; that the lower amplitude deflection train caused deeper adaptation ratios. This pattern was not observed in the trigeminal ganglia, but it was replicated in the thalamus and trigeminal principalis nucleus (PrV). By presenting test deflections at variable delays after the end of the stimulus train, it was also found that the lower amplitude train resulted in slower recovery from adaptation. Notably, however, these results avoided a potential source of coding ambiguity with the synaptic depression model that the authors had identified as possibly arising from intersecting adaptation curves from different stimulus amplitudes (see Figure 1B of Ganmor *et al.*, 2010, reproduced here as Fig. 1), leading them to propose that the adaptation patterns they had observed arising in the brainstem may serve to counterbalance such ambiguity by filtering out low intensity stimulation while preserving responsiveness to stronger stimuli.

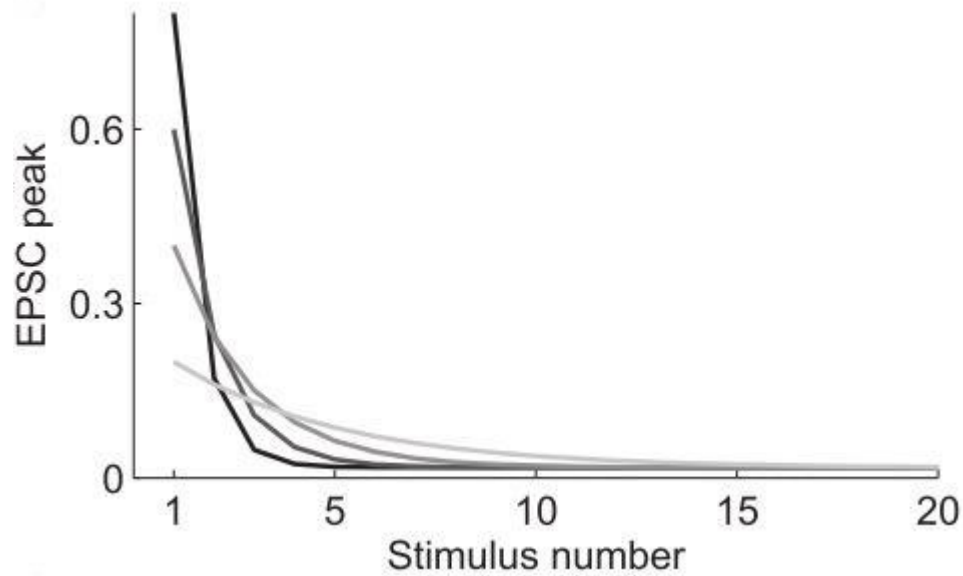


Figure 1: Theoretical adaptation curves for the responses to stimuli in a repetitive train, where stimuli were delivered as electrical stimulation of the pre-synaptic neuron. The curves show predicted curves based on different pre-synaptic firing probabilities, with darker colours indicating greater firing probabilities. Y-axis units are arbitrary. (Adapted from Fig. 1B of Ganmor *et al.*, 2010).

This strange activity in the PrV was further explored in a later publication from the same laboratory (Mohar *et al.*, 2013). This study replicated the previous unexpected findings in principal whisker stimulation of the PrV but found that the pattern predicted by the synaptic depression model was occurring in the interpolaris nucleus (SpVi, the point of emergence for the paralemniscal pathway) and intriguingly in the PrV during adjacent whisker stimulation. To explain this difference between principal and adjacent whisker adaptation in the PrV, Mohar *et al.* point to the projections from SpVi to PrV (Timofeeva *et al.*, 2004; Furuta *et al.*, 2008). The fact that PrV could show two different types of adaptation depending on the whisker being stimulated was taken as a sign that pre-synaptic mechanisms are at play in creating the surprising adaptation behaviour of the PrV.

A correlation between neurons' adaptation dynamics and their roles in sensory coding has been convincingly proposed for whisker-responsive regions of the trigeminal ganglia and brainstem trigeminal nuclei in a recent study (Lottem *et al.*, 2015). In this paper, it was found that during 20 ms whisker deflections neurons could be assigned to two functional classes, one exhibiting rapid adaptation such that only a single PSTH peak was observed and the other

slow adaptation in which several PSTH peaks of serially declining peak values were observed within the 20 ms period. These are in line with rapidly-adapting and slowly-adapting categories previously proposed for primary afferents (Zucker and Welker, 1969). Two candidate velocity-coding paradigms were proposed in this paper, with the neurons in these two classes being correlated with distinct roles in both. Interestingly, it was also shown that the proportional division of neurons between the two adaptation classes varied between the PrV, the caudal end of the SpVi, and the rostral end of the SpVi, suggesting a possible correlation between the adaptation behaviours of a brain area's neurons and the area's functional role in sensory processing.

Adaptation to Statistically Distributed Stimulus Intensities

A third important form of adaptation worth considering is adaptation of neurons to the statistical distribution of stimulus intensities (Petersen *et al.*, 2009). Investigations into adaptation in the auditory (Dean *et al.*, 2005) and the somatosensory (Garcia-Lazaro *et al.*, 2007) cortices have found that neurons responding to an on-going dynamic stimulus can exhibit shifting or scaling adaptation depending on the nature of the change in the stimulus. In Garcia-Lazaro *et al.*'s somatosensory study, recordings of cortical neurons were taken while the whiskers were stimulated with 200 Hz sinusoidal stimuli with periodic changes in wave amplitude. The amplitudes were drawn from a pool of 25 stimuli, of which a select range were designated as the high probability region (HPR) which would account for 80% of pseudorandom amplitude selections. When the HPR range was shifted to higher amplitudes within the pool without any change in the HPR's width, shifting adaptation was observed which was characterised by cortical neurons' dynamic ranges shifting to encompass the HPR's range (see Fig. 2). When the HPR was widened to provide broader variation while holding the HPR's mean constant, cortical neurons exhibited scaling adaptation wherein the dynamic range remained roughly constant while neuronal response v. stimulus amplitude slopes changed. The fact that similar observations were recorded in Dean *et al.*'s auditory study suggests that the mechanisms may be common across sensory modalities.

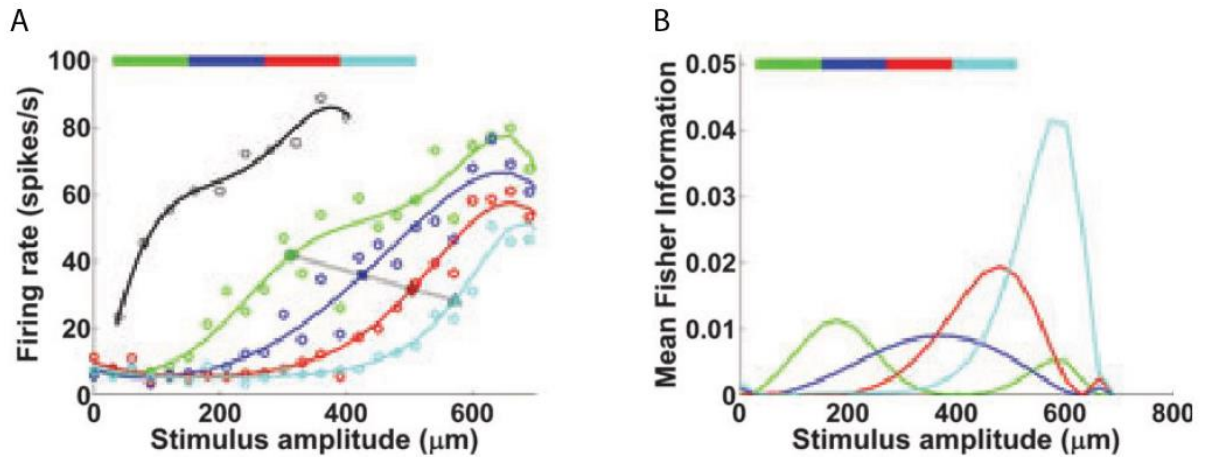


Figure 2: Neuronal response functions shift to encompass high-probability regions of stimulus distributions. *A:* Firing rates plotted against stimulus amplitudes. Open circles represent measured mean firing rates and curves are fifth-order polynomial fits. The black rate-level function represents responses of the non-adapted neuron. The four-colour bar at the top of the image represents the High Probability Region (HPR) amplitudes of the four different test conditions. The fitted rate-level functions are colour-coded to correspond with these test HPRs. The grey line connects the 50% response rate-values. *B:* Fisher information functions estimated from the fitted rate-level functions in *A*. (Adapted from Fig. 2 B & C of Garcia-Lazaro *et al.*, 2007).

An important investigation into the timescales of this form of adaptation comes from Lundstrom *et al.* (2010) who stimulated rats' whiskers with a varying stimulus envelope in which the standard deviation of whisker positions followed a sinusoidal profile. The firing rate response of cortical neurons displayed a similar sinusoidal profile with a period matching the stimulus sinusoid but with a phase lead. Such a phase lead is indicative of adaptive depression, because the adaptive reduction in response magnitudes will cause the firing rate to reach a peak before the stimulus intensity does and to reach a minimum before the actual stimulus intensity does. The degree of the phase lead was roughly constant at 44° across different stimulus sinusoid periods tested, meaning that the absolute timescales of this form of adaptation will vary with the periodicity of the stimulus variations.

A previous paper from the Neural Coding Group (Adibi *et al.*, 2013a) with relevance to this third form of adaptation found that neural response functions to pulses of varying amplitudes would adapt to a background of low amplitude stimulation by shifting thresholds to match the amplitude of the background stimulation. This is in agreement with investigations into the visual system of the blowfly (Calliphoridae family), which reported adaptive rescaling of H1 neuron input-output functions to match prevailing statistics of stimuli (Brenner *et al.*,

2000; Fairhall *et al.*, 2001). It is also consistent with the findings of a previous study in the rat barrel cortex (Maravall *et al.*, 2007). Such adaptive rescaling has also been documented as a rapidly acting (Dean *et al.*, 2008) adjustment for sound volume levels in the auditory midbrain (Dean *et al.*, 2005) and even primary auditory nerves (Wen *et al.*, 2009). The improvements this could bring to discrimination between stimuli near the adaptor amplitude suggest a role in explaining the results of previous psychophysical studies finding that human subjects asked to identify the more intense of two somatosensory stimuli were able to do so at lower amplitude difference thresholds when they had previously been exposed to an adaptor of similar amplitude to those used in the test (Goble and Hollins, 1993; Tannan *et al.*, 2007). This adaptive rescaling is in line with the hypothesis that adaptation serves a role in efficient coding, as maximum coding efficiency would be achieved if neural response distributions match the integral of stimulus distributions (Fig. 1; Wark *et al.*, 2007, reproduced here as Fig. 3; see also Fig. 4).

Perceptual role of adaptation

Detection v. Discrimination: Musall *et al.* 2014

To explore the perceptual consequences of adaptation in the somatosensory cortex, Musall *et al.* (2014) performed chronic recordings of cortical neurons in rats trained for a two-alternative forced choice task in which they obtained a water reward if they correctly identified which of two spouts to lick at based on which side of their face was receiving more intense whisker stimulation. When the investigators presented stimulus trains of between 1 to 4 deflections to a single side of the face, they found that the probability of a rat licking at the correct spout increased with deflection number, but not along the curve anticipated if post-initial deflections had equal perceptual weight to the initial one. Rather, the improvement followed a reduced improvement curve modelled on the measured adaptive

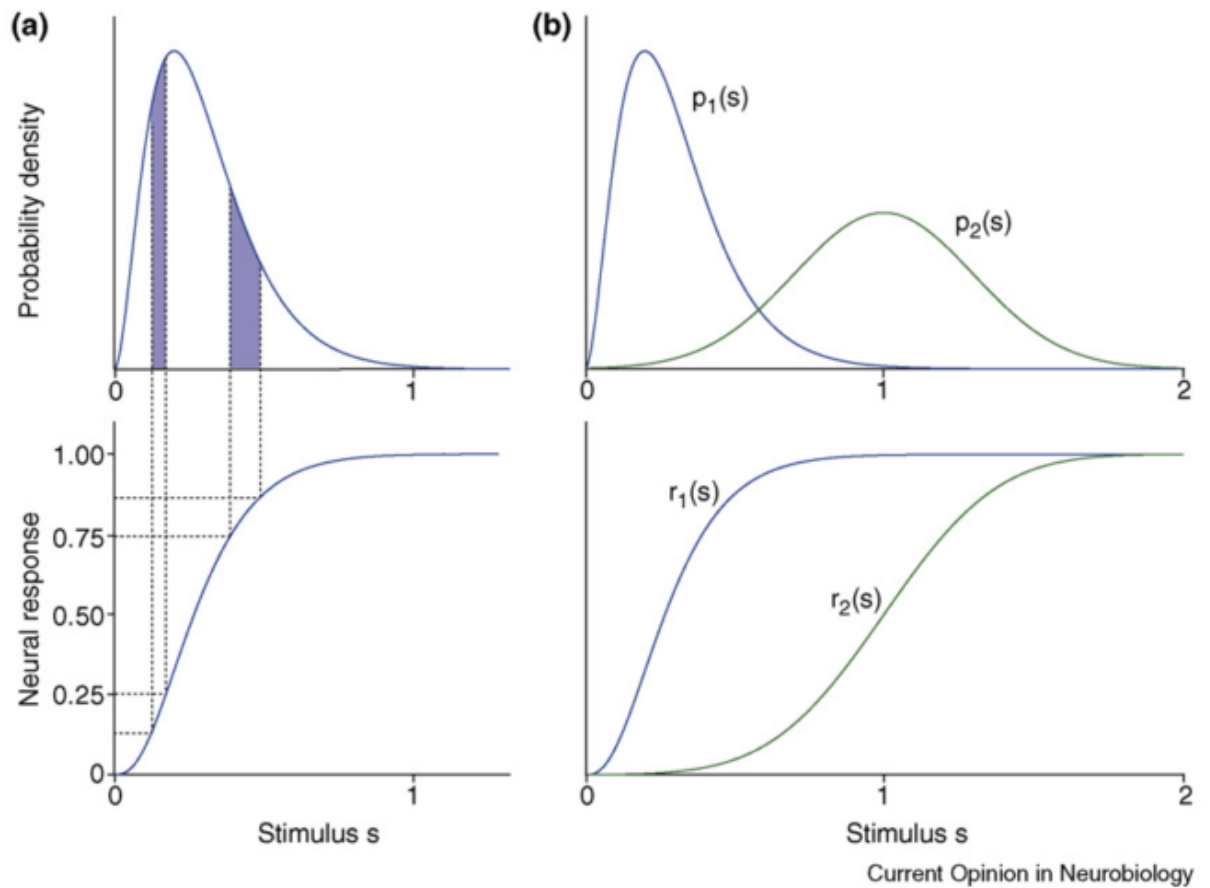


Figure 3: Adaptation as a mechanism for efficient coding. A: Given the distribution of stimulus intensities (top), the most efficient mapping onto neural response will be the integral of the stimulus distribution, as this mapping transforms equal probability in the stimulus distribution into equal response ranges. B: The stimulus and response distributions from the previous subfigure are shown in blue (p_1 and r_1). A changed stimulus probability distribution (p_2 , in green) will necessitate a changed mapping of responses (r_2 , in green), which is simply the integral of the changed stimulus probability distribution. (Adapted from Fig. 1 of Wark *et al.*, 2007).

attenuation of cortical responses to post-initial deflections. In contrast, when a similar experiment was performed using optogenetic stimulation to cause non-adapting cortical activity, performance improvements improved alongside increasing numbers of light pulses along a curve expected based on equal perceptual weight for each pulse in the train. To explore the effects of adaptation in discriminating between target and distractor stimuli, the authors conducted experiments in which both sides of the face were exposed to whisker deflection trains of one second duration, one side receiving the target and the other side a distractor train of lower deflection frequency. With whisker stimulation it was found that even a single distractor deflection in the one-second interval could significantly reduce correct discrimination even when the target train had a frequency of 40 Hz. When analogous

experiments were conducted with target and distractor optogenetic stimulus trains, however, it was found that the frequency of the distractor pulses had to approach half that of the target before causing notable reductions in discrimination performance. Based on these findings, the authors concluded that frequency-dependent adaptation of somatosensory cortex responses reduced the capabilities of rats in stimulus detection and discrimination tasks.

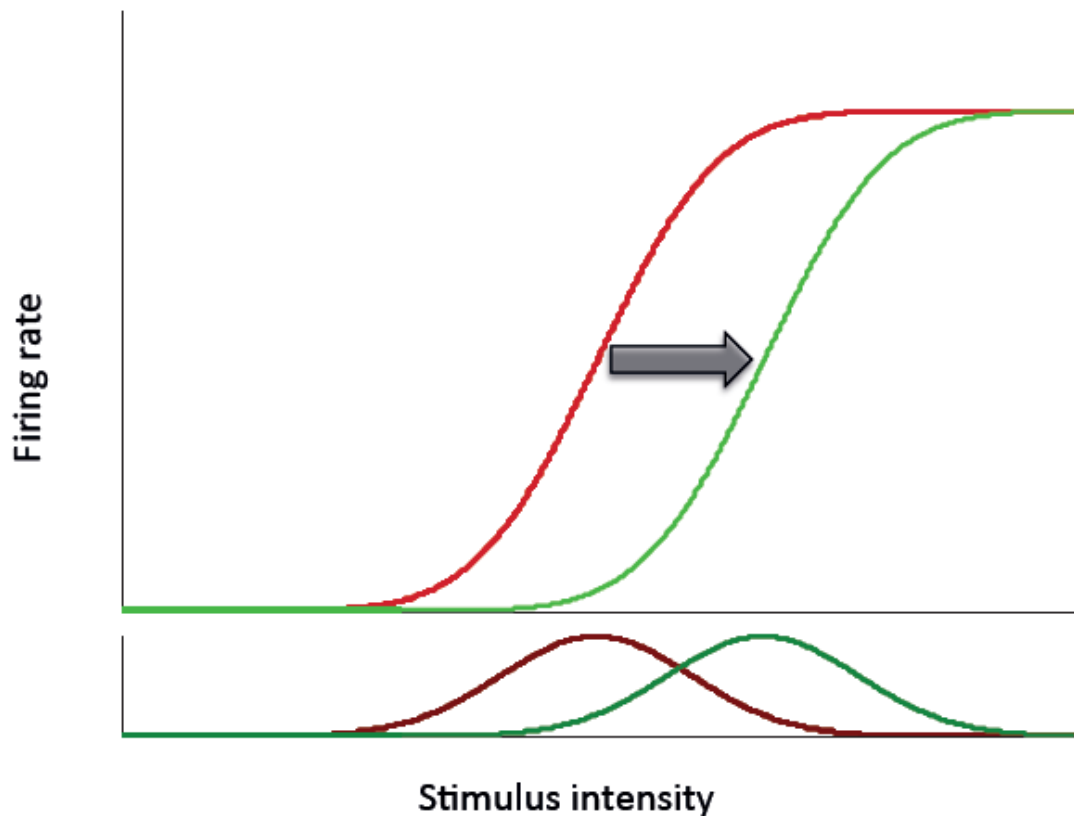


Figure 4. General schematic of how adaptive shifts in a neuron's input-output functions will vary according to prevailing stimulus statistics (Dean *et al.*, 2005, 2008; Adibi *et al.*, 2013a). The curves in the lower panel depict how capacity to discriminate between different stimulus intensities will vary in the two different adaptation states.

This finding left the question then of what benefit neuronal response adaptation provided that justified the reduced detection and discrimination capabilities. To probe this, the authors tested a new paradigm in which the somatosensory cortices of both hemispheres were activated by two-second stimulus trains, either by vibrissal deflections or optogenetic pulses (the mode being the same for both hemispheres), but with the train of one side containing a variable number of deviant pulses of greater intensity (greater deflection speed or light power),

known as the deviant stimuli, delivered in the last half-second of the train. The rats received a reward by licking on the spout corresponding to the side of the deviant stimuli. From the results, it was clear that the rats exhibited superior deviance detection in the case of whisker stimulation. The authors explained this by showing that adaptation in response to whisker stimulation caused a proportionally greater attenuation of responses to stimuli of non-deviant amplitude than to the deviant amplitudes. This had the effect of increasing the contrast between responses to the different stimulation intensities. Based on these results, the authors argue that adaptation serves to improve detection of changes in sensory input even at a cost in detection of persistent stereotyped stimuli.

Detection v. Discrimination: Ollerenshaw *et al.* 2014

Another study exploring adaptation's effects in detection and discrimination tasks came to similar conclusions. Ollerenshaw *et al.* (2014) used voltage-sensitive dye injections to study subthreshold population activity in L2/3 of S1 in anaesthetised rats using optimal detection theory within functionally identified barrels. In exploring the effects of adaptation on detection, the authors compared the performance of an ideal observer examining responses to single deflections presented either in a non-adapted state (at least 3.8 s of rest) or in an adapted state (after 1 s of a 10 Hz adaptor pulse) and found that the observer's detection performance was worsened in the adapted state. To study effects on discrimination, the authors placed piezo stimulators on two adjacent whiskers and simulated an ideal observer trying to determine which of the two whiskers had just been presented with a strong deflection, either in a non-adapted state or in an adapted state (previously described adaptor pulse delivered to both whiskers), and found that discrimination performance was in fact improved in the adapted state, with one factor being that adaptation reduced the size of the region showing increased activity following a whisker deflection.

To follow up these anaesthetised observations psychophysically, the authors performed analogous experiments involving rats being trained to understand whisker deflections as expressing instructions as to when to lick for a water reward following a 3

second auditory cue (with a variable time interval between the cue offset and the informative deflection). For the detection task, the rat was presented with deflections of variable velocity as *go* signals instructing them to lick for a reward (licking too early was penalised with a time-out period and light) with the rat being in either a non-adapted state (rest during the auditory tone) or an adapted state (12 Hz vibrissal stimulation concurrently with the tone). The psychometric curves for detection probability against deflection velocity showed that adaptation resulted in a rightward shift of the curve, meaning that the threshold velocity for detection had been raised. The curve showed some recovery to the non-adapted baseline for test deflections presented at longer temporal delays after the adaptor. For the discriminability task, the protocol was modified in that constant-velocity deflections were presented to two adjacent whiskers, deflections to one being *go* signals and to the other being *no-go* signals. Licks after deflection of the *go* whisker were rewarded with water while licks after the *no go* signal were penalised with a time-out and light. The authors found that the hit to false alarm ratio was improved when the rats had been exposed to an adaptor stimulus, suggesting adaptation did in fact improve the rats capability to discriminate between deflections to different whiskers. These findings provide clear evidence for an adaptive trade-off between detection and discriminability in spatial problems.

Detection v. Discrimination in Other Systems

Adaptation as a means of enhancing detection and discrimination of novel stimuli has also found support in studies from auditory cortex, with a study of cortical responses in awake rats finding that short-term adaptation to a standard frequency resulted in an increased spike rate response to a deviant stimulus (Behrens *et al.*, 2009). Similar experiments with anaesthetised cats found that cortical neurons recorded during a sequence of standard and deviant tones showed deeper adaptive attenuation to the standard tone, with a resultant improvement in discriminability of the two tones as compared to a sequence where the two were presented with equal probability (Ulanovsky *et al.*, 2003). Further experiments in the

auditory cortex have tended to further support a role for neuronal adaptation in this system serving to improve novelty detection capabilities (Malmierca *et al.*, 2014).

Whisking as Mechanism for Adaptation

It has even been proposed that whisking itself may be a mechanism to harness the enhanced sensory discrimination arising from adaptation (Moore, 2004). It has been observed that free whisking in air results in spiking activity along the vibrissal sensory pathway at the whisking frequency (Fee *et al.*, 1997; Leiser and Moxon, 2007), which may serve to put the pathway into an adapted state. Consistent with this view, a study of local field potentials in the rat barrel cortex (Castro-Alamancos, 2004) argued that sensory adaptation in rat barrel cortex is dependent on whether the rat is in an alert or quiescent state. As evidence of this, it was shown that response depression to an on-going stimulus was absent in alert rats. This was not, however, due to strong responses throughout the train so much as suppressed responses to initial stimuli. In other words, cortical neurons of alert rats were in an adapted state from the beginning. This was shown in anaesthetised rats (where alert status was simulated by stimulating the brainstem reticular formation) and in comparisons of chronically recorded barrel cortex responses in rats as they transitioned between periods of sleep, awake immobility, and awake exploration of their own volition (where whisker stimulus trains were delivered by electrical stimulation of the whisker pad). The behaviour-dependency of adaptation was further explored through an active avoidance task in which rats were trained to avoid an aversive stimulus cued by a stimulus train delivered to the whisker pad. Intriguingly, it was shown that cortical adaptation during the train presentation was absent while the rat was learning the task but present after the rat had mastered the task. These results suggest a role for sensory adaptation in focus and attention, with the elevated responses seen in unadapted states perhaps functioning as a “wake-up” call to a quiescent animal, consistent with the previously discussed papers that argued for stimulus detection capabilities being greater in the non-adapted state. Subsequent computational studies of this relationship

between adaptation effects and brain state have suggested that it may play a critical role in determining emergent cortical activity patterns (Benita *et al.*, 2012).

The notion of the adapted state being the norm for neurons during wakefulness receives further support in investigations in the somatosensory cortex of awake rabbits (Swadlow *et al.*, 2005). Swadlow and Gusev (2001) took chronic extracellular recordings from both excitatory neurons in the VPM and FS interneurons in S1 receiving direct excitation from the thalamic cells. In studying the excitation of the cortical interneurons during periods of awake immobility for the rabbits, they found that spikes in the VPM were more effective in eliciting action potential responses in the cortical interneurons when the interval since the thalamic neuron's previous spike was relatively long, suggesting a recovery from a state of adaptation. Extending their investigation from a local view of single cortical neurons to a global view of effects on the overall cortex, Swadlow *et al.* (2002) simultaneously recorded the action potentials of thalamic neurons by way of extracellular recordings and extracellular synaptic currents of cortical populations by way of current source-density analysis. Again they found that increasing intervals between VPM spikes and their immediate predecessors resulted in stronger responses, in this case consisting of enhanced field potential responses in L4 and L6, which would be consistent with enhanced responses associated with the non-adapted state serving as a "wake-up" call to the quiescent animal.

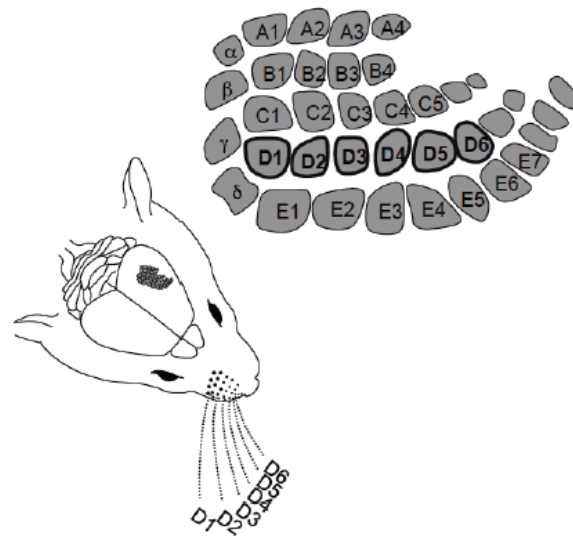
This is further supported by the findings of an earlier study using chronic extracellular recordings to study barrel cortex and VPM responses to tactile stimulation in awake rats (Fanselow and Nicolelis, 1999). They found that both cortical and thalamic spike rate responses to vibrissal deflections (applied via cuff electrode stimulation of the infraorbital nerve) were reduced during whisking as compared to the quiet state. Notably this reduction was not observed when the rat was engaged in non-vibrissal motor activity, indicating that the reduction was a specific result of whisking activity. When pairs of identical stimuli presented at variable temporal separation were applied, statistically significant suppression of responses to the second stimulus of the pair was observed in the quiet state in both cortical and thalamic

stations, particularly at intervals of 75 ms or less. By contrast, during whisking no statistically significant paired pulse suppression was observed. These observations are consistent with a view that neuronal responses in the quiet state are beginning from a non-adapted state but those during whisking are the result of neuronal populations already in an adapted state due to vibrissal motion. Similar reductions in stimulus responses during whisking as compared to quiescent animals as well as a lack of further adaptation of neuronal responses during whisking were also reported in a later study using mice (Crochet and Petersen, 2006).

Aims of the Current Thesis

To contribute further insights to the dynamics and mechanisms of cortical adaptation, I performed experiments to quantify the time-course of recovery from adaptation and explore how said time-course of recovery is affected by the nature of the adaptor stimulus. The barrel field of the somatosensory cortex (Fig. 5 A) offers a convenient avenue for such experiments owing to the discrete representation of individual whiskers within columnar functional units (Fig. 5 B) (Woolsey and van der Loos, 1970; Welker, 1976; Simons, 1978; Simons and Woolsey, 1979).

A



B

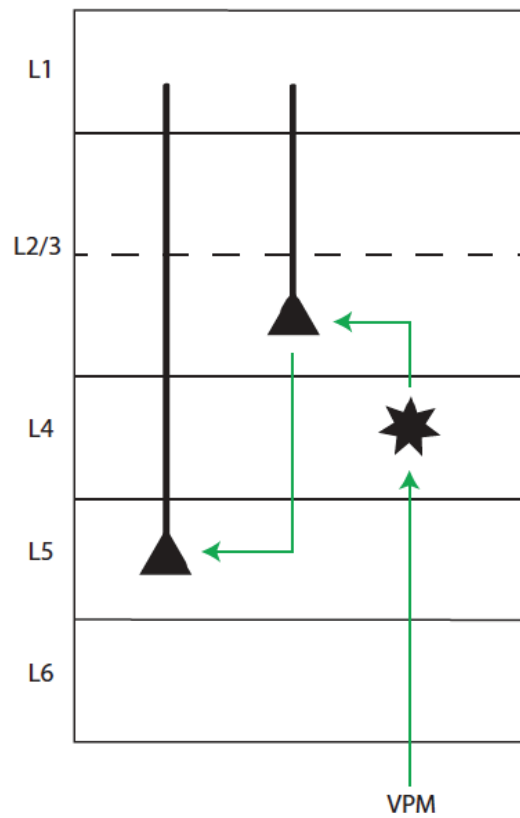


Figure 5. A: Anatomical diagram of the barrel cortex and correspondence between barrel layout in somatosensory cortex and vibrissa layout on mystacial pad. B: Simplified diagram of laminar structure of cortex and information flow along lemniscal pathway.

Experimental Methodology

Animal preparation and surgery: The model animals for this research were male Wistar rats between the ages of 4 and 6 weeks. All experiments with animals were conducted with approval of the Australian National University's animal ethics committee and with accordance to Australian Capital Territory and Australian federal laws and regulations. A total of 43 rats were used, with a full protocol recording being achieved for at least one neuron in 30 rats. A total of 61 neurons were juxtacellularly recorded across two experiments (30 neurons in Experiment one, and 31 neurons in Experiment two).

Each rat was anaesthetised with intraperitoneal injection of urethane (1.5 g/kg). Appropriate depth of anaesthesia was judged based on loss of the toe pinch reflex, which confirms stable surgical anaesthesia (Rojas *et al.*, 2006), being extinguished at greater anaesthetic doses than several other reflexes (Field *et al.*, 1993). The toe pinch reflex was periodically checked throughout the surgery, but as urethane is a long-lasting anaesthetic (Hara and Harris, 2002), additional doses were unnecessary. At this point the skin and muscles over the top of the skull were cut away to expose the bone. Wound margins were not infiltrated with any local anaesthetic, as loss of the toe pinch reflex is generally accepted as indicating depth of anaesthesia adequate for surgery (Committee on Rodents, 1996). The animals were not artificially ventilated. Physiological monitoring consisted of a rectally-inserted thermometer probe connected to a heating blanket.

The rat's skull was then attached to a custom-built stereotaxic frame using dental cement and stainless steel screws embedded into the bone. A craniotomy of ~1.5 mm radius was performed over the barrel cortex, centred 2.5 mm posterior and 5.5 mm lateral from bregma, after which a small incision was made in the dura to allow the recording pipette to enter the brain. The pipette was pulled from borosilicate glass and had an impedance of 5 to 10 M Ω . The pipette was held with an HL-2 electrode holder for a Dagan (Minneapolis, MN)

headstage 7001 connected to a BVC-700A bridge and voltage clamp amplifier. At the time of insertion the pipette had an internal pressure of 300 mmHg, though this was immediately reduced to 20 mmHg. After the pipette was inserted, a layer of agarose gel was applied to the craniotomy to prevent desiccation and brain tissue pulsation.

Cell recording: Experiments were performed using the juxtacellular methodology, a loose-patch single-cell technique for recording electrophysiological data at the membrane of cells in an anaesthetised animal and staining cells with Neurobiotin by way of nanostimulation-induced electrophoresis (Pinault, 1996). The pipette was lowered through the brain at 20 mmHg internal pressure with 1 nA current pulses applied in an alternating pattern of 200 ms of current followed by 200 ms of no current. Voltage responses were monitored in AxoGraph X (AxoGraph Scientific, Sydney, Australia) at a sampling rate of 35 kHz, with a fourfold or greater increase in impedance taken to indicate contact with a neuron. Pressure was released at this point and pipette was lowered further only insofar as was necessary to achieve action potential recordings of 1 mV apparent amplitude or greater. The pipette was loaded with artificial cerebrospinal fluid with 1% Neurobiotin.

Whisker stimulation: Sinusoidal whisker deflections were delivered onto a neuron's principal whisker by way of a piezoelectric filament whose motion could be controlled by voltage output from an NI card (National Instruments, Austin, TX) (Fig. 6 A). The piezoelectric filament was calibrated using an OPB819Z optical sensor (OPTEK Technology, Carrollton, TX). At the outset of an experiment, whiskers were trimmed to roughly fifteen mm in length. This reduced length aided insertion into the needle, but also provided the advantage of working exclusively with the proximal region of a whisker that behaves as a rigid body (Knutsen et al., 2008; Quist, *et al.*, 2014). Due to the conical tapering of vibrissae, events at the less rigid distal regions exert fundamentally different forces and motions at the whisker base from those at more proximal regions (Quist *et al.*, 2014), with bending stiffness decreasing from base to tip over five orders of magnitude (Hires *et al.*, 2013) and whiskers often showing some bending out of the plane of a distal force (Huet *et al.*, 2015), so that distal

deflections will not be faithfully represented at the base. Whiskers were threaded in so that the end of the needle was no further than 2 mm from the mystacial pad, as external object contacts cause a higher velocity whisker deflection the closer they are to the vibrissal base (Lottem *et al.*, 2015). Due to clear evidence in the literature of cortical neurons being directionally selective in their deflection responses (Simons and Woolsey, 1979; Bruno, *et al.*, 2003), no consistent piezo orientation was used. Rather, the piezo orientation was selected on a case-by-case basis to maximise each neuron's responses. All detection, sorting, and analysis of action potentials were carried out in MatLab R2014b (The MathWorks, Natwick, MA).

Spike detection: During offline analysis, voltage recordings were first subtracted by their mean to remove any offset from a baseline average of zero. A high-pass filter of order 2 with a 3-dB frequency of 300 Hz then applied using the 'N.F3db' specification of the `fdesign.highpass` function in MatLab. Spikes were then identified based on a peak exceeding 0.3 mV and a spike width above this threshold of at least 143 μ s. This width threshold was sufficient to capture even fast-spike units, which tend to have half-widths around 150 μ s (Cardin *et al.*, 2009).

Confirmation of responsiveness: For all tests, whisker deflections were of a constant duration of 24 ms and a variable amplitude at an inter-trial interval of 1.5 seconds. Eleven amplitudes were presented, including a zero-amplitude negative control for measuring background firing, with pseudo-random shuffling of the eleven amplitudes in interleaved trial blocks for 35 trials. Variable deflection amplitudes combined with constant durations translates into variation of deflection velocity, which a study of L4 cortical responses to sinusoidal whisker deflections found to be the kinematic feature most reliably encoded in neuronal firing (Arabzadeh *et al.*, 2004). The response to a deflection was measured within a 50 ms window beginning at the onset of the deflection, rate coding being well-documented in barrel cortex (Ahissar *et al.*, 2000; Panzeri *et al.*, 2001; Arabzadeh *et al.*, 2004; Foffani *et al.*, 2004; Arabzadeh *et al.*, 2006) (Fig. 7 A). Such analysis based on a spike count within a post-stimulus window is widely used classic method of exploring neuronal encoding of stimuli (Petersen *et al.*, 2009) and has been

shown to robustly co-vary with discrimination behaviour of awake animals (Luna *et al.*, 2005). Responses were averaged across trials and for each non-zero amplitude a Student's *t*-test was performed against the zero amplitude to test for a statistically significant positive response (example shown in Fig. 7 B). If one was detected, further experiments were performed with the selection of an amplitude exhibiting an appropriately robust effect. No *a priori* assumptions could be made about the appropriate stimulus parameters to drive a response in a given cortical neuron, owing both to directional selectivity in barrel cortex neurons (Wilent and Contreras, 2005) and to the interplay of both excitatory and inhibitory inputs differentially activated at different stimulus intensities (Swadlow, 2002, 2003).

Staining: Once experiments on a neuron were completed, the neuron was nanostimulated by application of 200 ms pulses of current of sufficient intensity for entrainment interspersed by 200 ms of no current. The level of current that needed to be applied varied, but was usually not much greater than 10 nA. This continued until a widening of action potentials indicated loading of Neurobiotin. At the end of the day the rat was perfused with 4% paraformaldehyde in phosphate-buffered saline. The brain was allowed to sit in solutions of sucrose and paraformaldehyde until it sank in a 30% sucrose solution. The brain was then cut into 120 micron sections on a cryostat, incubated in a 0.1% Triton-X in PBS solution for five hours, incubated overnight in 0.1% Alexa Fluor 488 antibody and 0.1% Tween-20 solution, then mounted onto slides and visualised using a confocal microscope (Nikon Instruments, Melville, NY). An example image of a stained neuron is shown in Fig. 6 B.

Paired pulse paradigm: Test stimuli were presented at variable delays after the offset of an adaptor stimulus. Test pulses were presented at an interval of at least 2.1 seconds from each other, with adaptor pulses being inserted into the sequence as appropriate to create the desired adaptor-test separation. At no point was the separation between the adaptor onset and the test pulse immediately preceding it allowed to fall below 1 second. Admittedly, though,

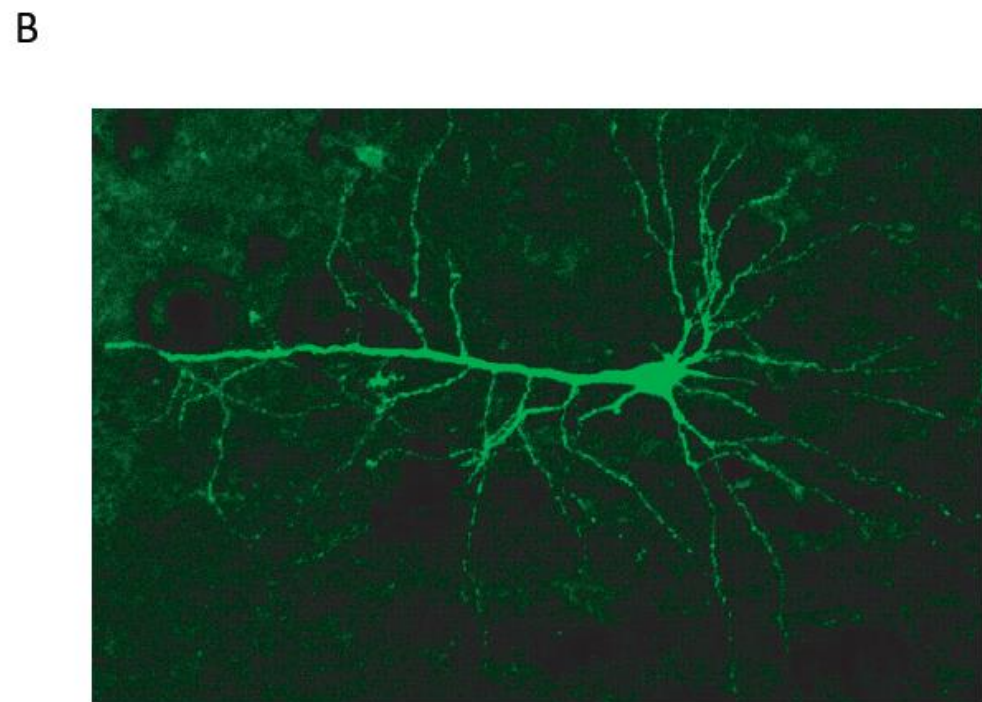
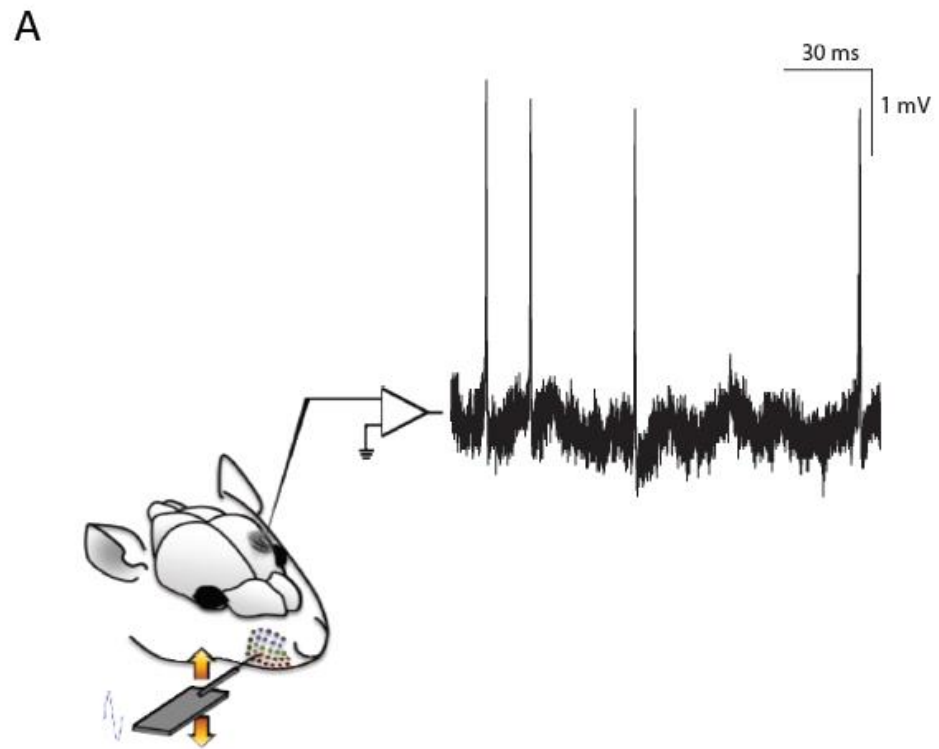


Figure 6. A: General schematic of juxtacellular recordings during whisker-deflections. Example spikes shown from raw data. B: Example of histologically recovered neuron.

there were some cases of neurons observed with incomplete recovery at 1.5 seconds (see Fig. 9 C & D), so if this study were to be repeated it would be advisable to extend that minimum gap to 2 seconds. A control was necessary to distinguish between changes in a neuron's response to test stimuli due to adaptation and changes in its background firing rate during the same period. To provide this control, for each adaptor that was used an interval occurred in which the adaptor was presented without a test deflection, thus allowing an opportunity to measure changes in background firing rates. To determine the change in firing rate due to the presence of a test stimulus, the firing rate within the test pulse's measuring window was subtracted by a count of APs within a temporally equivalent window for the adaptor-sans-test control (Fig. 8 B & C, Fig. 17 B & C). By way of positive control, a test deflection would be presented without any recently preceding stimuli. To correct for the problem of background spikes previously discussed, a negative control was used which constituted the presentation of an interval without any piezo deflections. The adjusted positive control was thus calculated by an analogous subtraction (Fig. 8 A, Fig. 17 D). A statistically significant difference, by Student's *t*-test, between the measurements for the positive and negative controls was a pre-requisite for data from the neuron being incorporated into the overall data set. A neuron's response to a post-adaptor test deflection at separation k (AI_k for **Adaptation Index at k**) could thus be normalised by the following equation:

$$(1) \quad AI_k = \frac{F_k - F_c}{C_{pos} - C_{neg}}$$

where F_k is the firing rate after presentation of the test deflection, F_c is the firing rate for a temporally equivalent post-adaptor window without a test deflection, C_{pos} is the firing rate in response to the positive control, and C_{neg} is the firing rate during the temporally equivalent period of the negative control, such that an *AI* value of 1 represents firing identical to a non-adapted state, a value below 1 indicates firing suppression, and a value above 1 indicates facilitation (Fig. 8 D, E, & F). All control and adaptor conditions were performed with pseudo-random shuffling in interleaved trial blocks for a target of 50 trials (though fewer might be

A

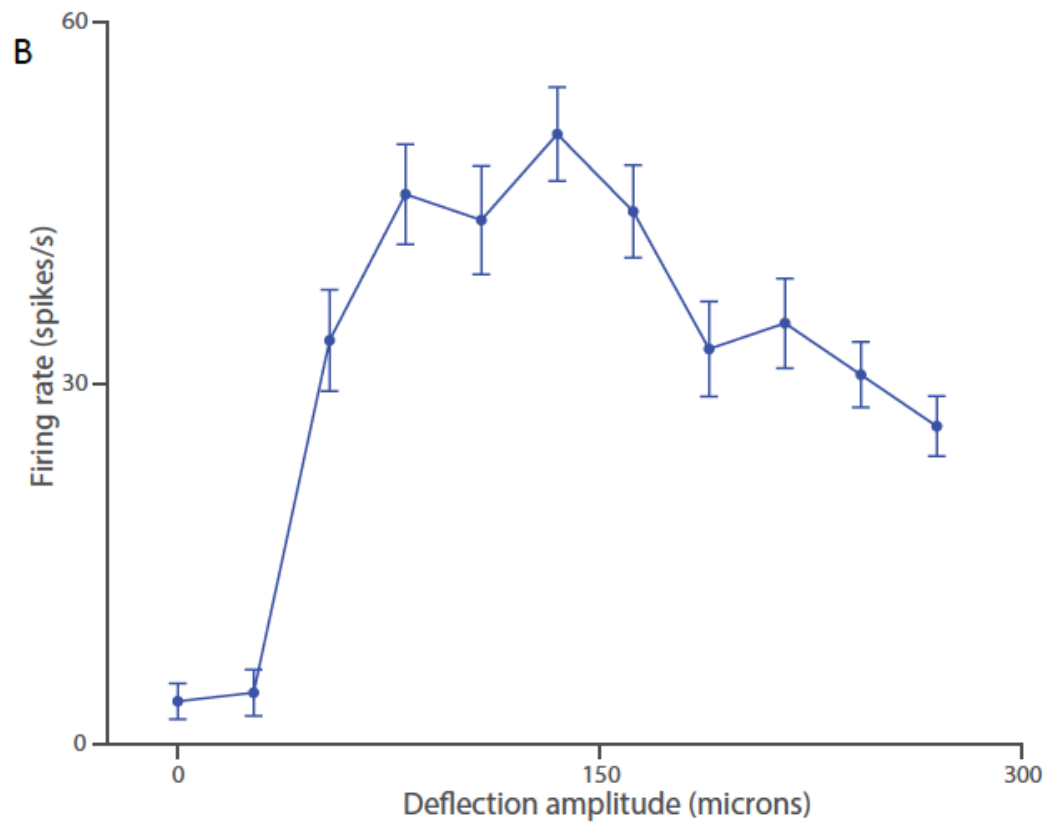
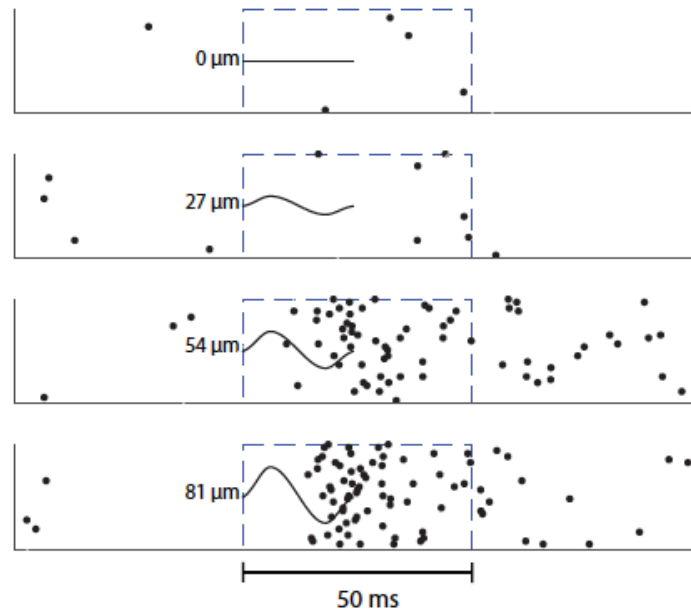


Figure 7. A: Raster plots for a sample neuron demonstrating the change in responses as deflection amplitudes are increased. Blue boxes indicate the bounds of the response quantification window. Superimposed sinusoids are scaled on the x-axis to faithfully represent the time-course of piezo deflections. Amplitudes to the left are half-amplitudes, the distance between a peak and the mid-point of the wave. B: Averaged response of a sample neuron to sinusoidal deflections of varying amplitude. As before, amplitudes are half-amplitudes. Error bars are standard error.

used if the neuron was lost before 50 trials could be performed). More trials were used here than for the initial confirmation of whisker responsiveness, as more data were desired for proper statistical analysis of adaptation behaviours. Note that these firing rates were calculated by trial-by-trial subtractions followed by taking a mean, but that taking the mean first and then doing overall subtractions yielded the same result.

Sigmoid fitting: The sigmoid fit for the data in Fig. 19 A was prepared in Matlab R2014b using the “fit” function and the following equation:

$$(2) \quad AI_t = \frac{P_l - P_u}{1 + \left(\frac{t}{t_c}\right)^k} + P_u$$

where t is a log-scale time-point, AI is an adaptation index at time t , P_l and P_u are lower and upper plateaux, respectively, t_c is the midpoint of the sigmoid, and k is a power constant.

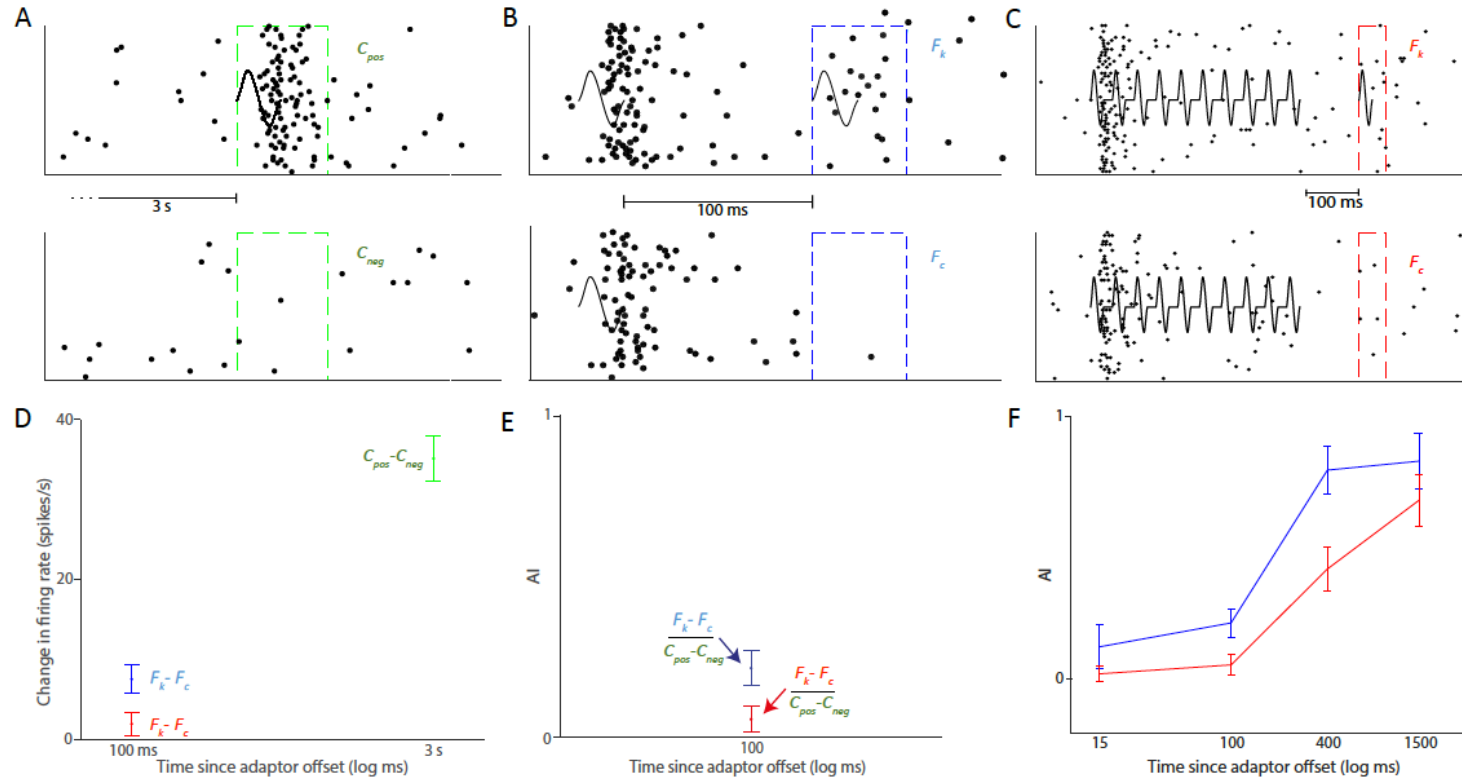


Figure 8. A-C: Schematics for Experiment One protocol and background firing correction. Quantification windows for test response (top) and background correction (bottom) are indicated in green (A), blue (B), or red (C) boxes. Superimposed sinusoids are scaled on the x-axis to faithfully represent the time-course of piezo deflections. A: Positive (top) and negative (bottom) non-adapted control conditions. B: Single pulse adaptor condition, showing sample adaptor-test temporal separation. C: Ten pulse adaptor conditions, showing sample adaptor-test temporal separation. D: Plot of changes in firing rate for A-C, each point representing the difference between number of spikes present in the positive control (A) or test present (B-C) conditions and the number present in their respective negative control (A) or test absent (B-C) conditions. E: Demonstration of normalisation to produce an Adaptation Index. F: Adaptation recovery time-course plots for both single pulse (blue) and ten pulse (red) adaptor conditions. All error bars are standard error.

Fano factors: A Fano factor is a measure of response variability, defined mathematically as follows:

$$(3) \quad F = \frac{\sigma^2}{\mu}$$

where σ^2 is the variance and μ is the mean within a defined time window.

Signal detection theory: To explore the capacity of an ideal observer to discriminate between the presence or absence of a whisker deflection, receiver operating characteristics (ROC) analyses were performed based on signal detection theory (Green and Swets, 1966; Adibi and Arabzadeh, 2011). Areas under the ROC curves (AUROC) are then taken as an index of discriminability between test present and test absent conditions.

Experiment 1

One prediction stemming from the short-term synaptic dynamics hypothesis is that more intensive adaptor stimuli should result in a greater depth of adaptation requiring a longer recovery time (Zucker, 1989; Tsodyks and Markram, 1997; Ganmor *et al.*, 2010; Cho *et al.*, 2011). As far back as 1926, Adrian and Zotterman observed time-courses of adaptation behaviours showing dependence on the strength of the adaptor, and studies of cortical activity elicited by whisker deflections trains have demonstrated adaptation to frequency-dependent steady states (Khatri *et al.*, 2004; Musall *et al.*, 2014). I predicted that the time-course of recovery from adaptation should likewise be dependent on the intensity of the adaptor stimulus. Recordings were performed from 32 barrel cortex neurons in 17 different rats, with depth below the pia mater ranging from 600 to 1700 microns. For each neuron a sinusoidal deflection amplitude was selected that could be shown to evoke a positive control response, a non-adapted control consisting of a deflection presented after at least 3000 ms of silence, with a statistically significant elevation over a negative control of zero stimulation (Fig. 7 B, 8 A). Sinusoidal test deflections were delivered at adaptor-test separations of 15, 100, 400, and 1500 ms, with preceding adaptor being either a single sinusoidal pulse of identical parameters as test deflection (Fig. 8 B) or ten such deflections delivered at 25 Hz (Fig. 8 C), a frequency that falls within the normal range of a rat's whisking during palpation of an object (Berg and Kleinfeld, 2003). Both test and positive control responses were corrected by subtracting off a measurement of background AP firing during a temporally equivalent post-adaptor window (Fig. 8 D). Normalisation of test responses was then performed by dividing the background corrected test response by the background corrected positive control (Fig. 8 E), producing an Adaptation Index (Equation 1). This allowed a determination of adaptor-specific recovery time-courses for individual neurons (Fig. 8 F, Fig. 9 A-D). The majority of neurons (30 out of 32) showed a statistically significant depression of test responses, which in some cases showed clear dependence on adaptor condition (e.g. Fig. 9 A) and in other cases did not appear to be

dependent on number of adaptor pulses (e.g. Fig. 9 C). In some cases a statistically significant facilitation of firing rate could be observed (e.g. Fig. 9 B). Given the subtraction of background firing rates, it was also possible for Adaptation Indices to be negative (e.g. Fig. 9 D), indicating that the presence of a test deflection was not only failing to produce an elevation of firing rate but also producing a depression of the background firing rate that would otherwise be higher.

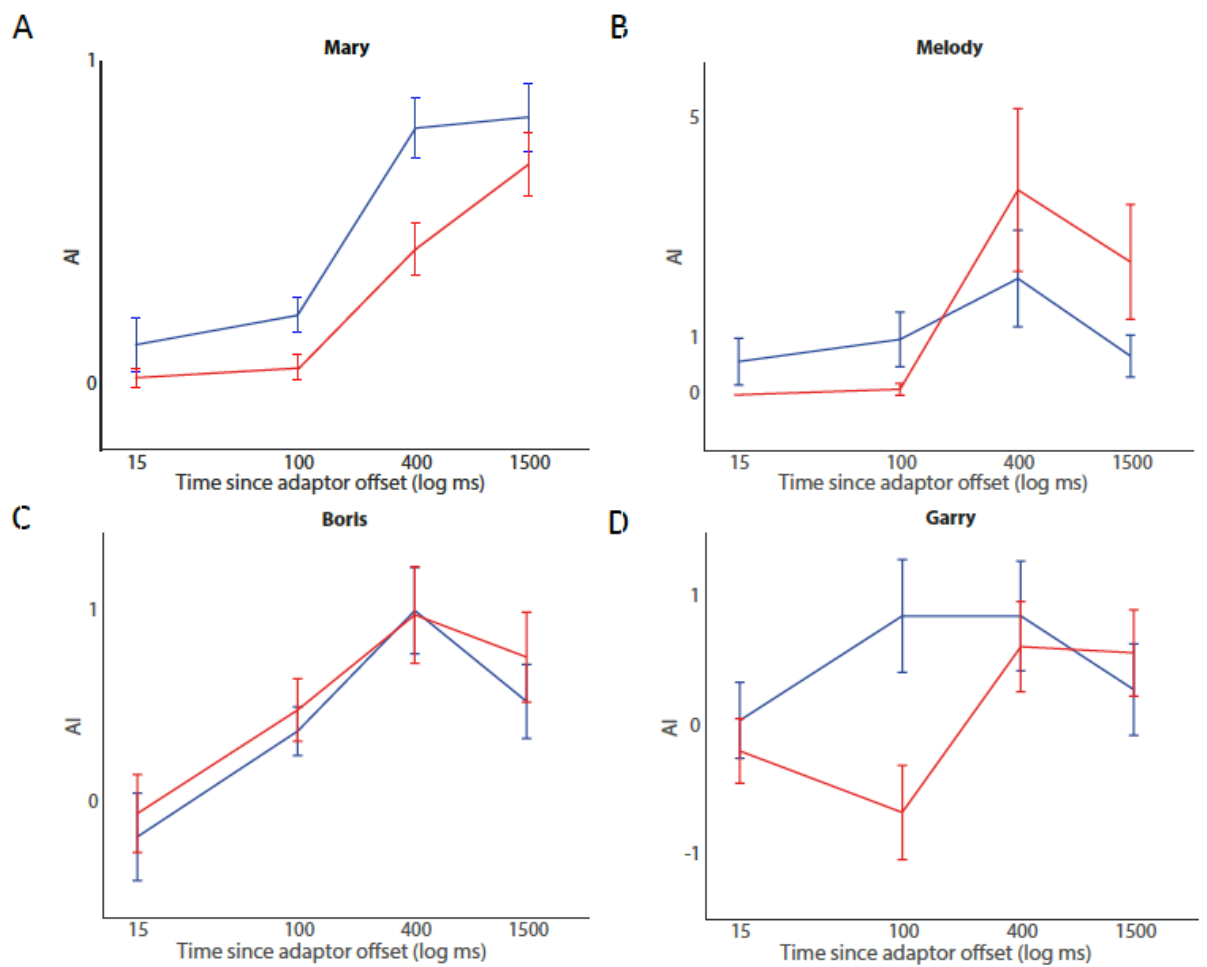


Figure 9. Adaptation recovery time-course plots for four example neurons, showing both single pulse (blue) and ten pulse (red) adaptor conditions. Error bars are standard error.

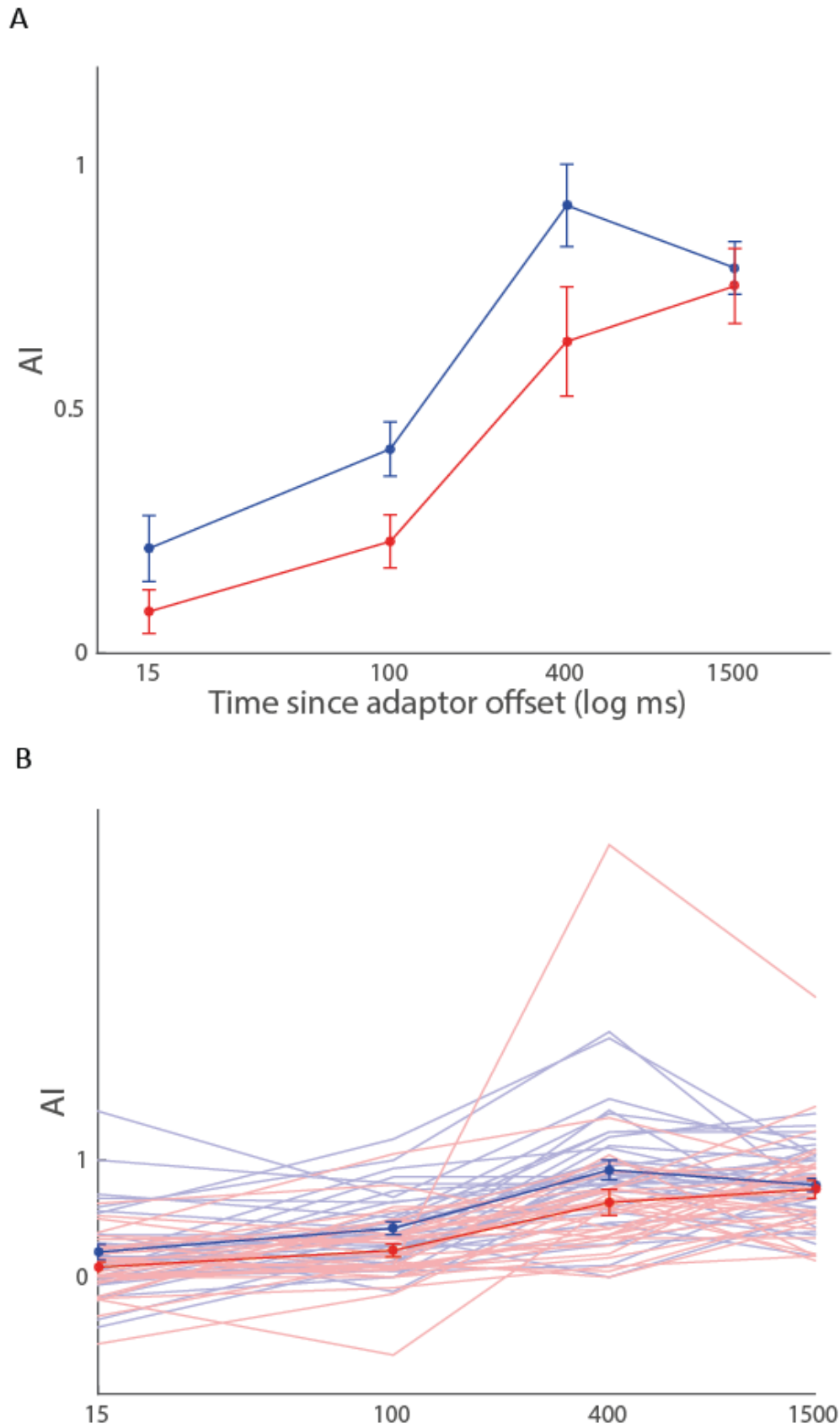


Figure 10. A: Population average ($n = 32$ neurons) for adaptation recovery time-courses, showing both single pulse (blue) and ten pulse (red) adaptor conditions. Error bars are standard error. B: Population averages (opaque colours) plotted alongside adaptation recovery time-courses for individual neurons (transparent colours).

When normalised test responses across the population were pooled and averaged, I observed there was indeed a greater degree of recovery from the less intense adaptor over hundreds of milliseconds when examining the averaged data (Fig. 10 A). ANOVA results confirmed statistically significant effects of both adaptor-test separation ($p < 10^{-21}$) and the adaptor length ($p < 0.002$). From Fig. 10 A, it is clear that adaptor-dependent differences in recovery time-course had worn off by 1.5 seconds. However, in the process of gathering these data it became obvious that while averaged responses displayed an unremarkable pattern of adaptor intensity-dependent recovery from adaptation (Fig. 10 A), individual neurons showed a considerable diversity of responses (Fig. 10 B). The discriminability in the averaged data is achieved in spite of the diversity of individual neurons' behaviours.

To further visualise these data, I prepared scatterplots, one for each separation, in which the normalised response of a neuron to a test deflection after a ten pulse adaptor is plotted against its normalised response after a one pulse adaptor (Fig. 11 A). The blue diagonal line in these scatterplots represents an equity line where normalised responses are equal regardless of the adaptor condition, and the red lines mark the border between adaptive depression and adaptive facilitation of neuronal responses relative to control responses. At 15 and 100 ms the dots are clustered within the red box, indicating adaptive depression, with some slight skew of dots to the right, indicating greater normalised responses after the one pulse adaptor. At 400 ms the dots are no longer clustered within the red box but are still showing a skew in the right-hand direction. At 1500 ms the dots are now centred more towards the intersection of the red box and blue line with no clear average skew in any direction, which is the expected observation in the case of recovery from adaptation.

To further explore this diversity, in particular diversity in how the intensity of the adaptor condition affected adaptation, a calculation was made of adaptor-dependent time-course differences for individual neurons by subtracting the Adaptation Index (Equation 1) of a test response after a single pulse adaptor by that recorded after a ten-pulse adaptor. For each of the four adaptor-test separations, a histogram was plotted showing the distribution of the

Adaptation Index differences (Fig. 11 B). Due to the nature of this subtraction, a result of zero indicates a neuron exhibiting equal response magnitudes after either adaptor condition, a positive result indicates greater normalised responses after the one pulse adaptor, and a negative result indicates a greater normalised response after the ten pulse adaptor. As expected from Fig. 10 A, the histograms show a distribution skewed in the positive direction for the first three separations but show a distribution more evenly distributed around zero at 1500 ms separation. This distribution pattern is more clearly illustrated in Fig. 12.

Continuing to work with these Adaptation Index differences, they were next plotted against a neuron's adjusted control firing rate for each of the four adaptor-test temporal separations used (Fig. 13 A). The motivation for this comparison is that previous studies of cortical neurons have reported distinct processing roles for regular-spiking and fast-spiking neurons (Atencio and Schreiner, 2008). At each of the four temporal separations, the scatterplot shows a tighter clustering of dots around the blue equity line at higher control firing rates, suggesting that distinct recovery patterns for the two different adaptor conditions are more a feature of neurons with low to moderate control firing rate than those with a high control firing rate. This relationship between control firing rates and Adaptation Index differences is better illustrated by plotting the absolute values of all differences against control firing rates, as in Fig. 13 B. For all four adaptor-test temporal separations in Fig. 13 B, a negative correlation occurs (for 15 ms, Pearson's $R = -0.10$; for 100 ms, $R = -0.20$; for 400 ms, $R = -0.25$; for 1500 ms, $R = -0.12$) but these correlation coefficients are not significant (for 15 ms, $p = 0.57$; for 100 ms, $p = 0.28$; for 400 ms, $p = 0.17$; for 1500 ms, $p = 0.53$).

Those dots in Fig. 13 A plotted in orange indicate neurons for which the Adaptation Index of a test response after either or both adaptor conditions exhibited facilitation. At a temporal separation where the neuronal responses return to a non-adapted state the expected result would be an increasing number of orange dots owing simply to the distribution of Adaptation Indices for either adaptor condition being centred around an average of 1, and indeed we see that the results are approaching such a condition in the scatterplot for the 1500 ms condition.

For the 15 and 100 ms scatterplots we see few orange dots, and this is again what we'd expect, this time owing to simple fact of adaptive depression being in effect. A more interesting result can be seen in the 400 ms scatterplot, where we have an increasing number of orange dots, but their distribution is clearly skewed in the positive y-direction, which makes sense because we'd expect facilitation (or at least a return to a non-adapted state) to be more readily achieved after the shorter adaptor. The fact that facilitation effects at 400 ms are observed in neurons with lower responses to control is interesting, and may be related to literature reports that facilitation of synapses is more commonly observed in synapses with a low probability of neurotransmitter release (Abbott and Regehr, 2004).

In addition to reducing the magnitudes of stimulus responses, adaptation is known to increase trial-to-trial variability of responses to stimuli (Adibi *et al.*, 2013a, 2013b). In order to quantify these effects, I calculated a Fano factor (Equation 3) for the positive control and each test condition of each neuron. In Figure 10, for each adaptor-test separation the Fano factors are plotted against background-corrected test responses for both adaptor conditions of each neuron. As the temporal separation increases from 15 ms through to the positive control of a test deflection presented at least 3 s after the most recent deflection, the Fano factors decrease as the response magnitudes increase (Fig. 14 A-E), a pattern that is borne out when average Fano factors are plotted against temporal separation for both adaptor conditions (Fig. 14 F). It is worth noting, however, that no clear statistically significant difference between Fano factors for the two different adaptor conditions was manifest in these data.

With response magnitude decreased and trial-to-trial variability increased, it now becomes worth asking how adaptation is impacting the capability of neuron's to distinguish between the presence or absence of an adaptor stimulus. This quantification of presence/absence discriminability is achieved through signal detection theory. The first step of signal detection theory is to consider how often an ideal observer, watching action potentials in a defined temporal window, would achieve hits and false alarms based on a

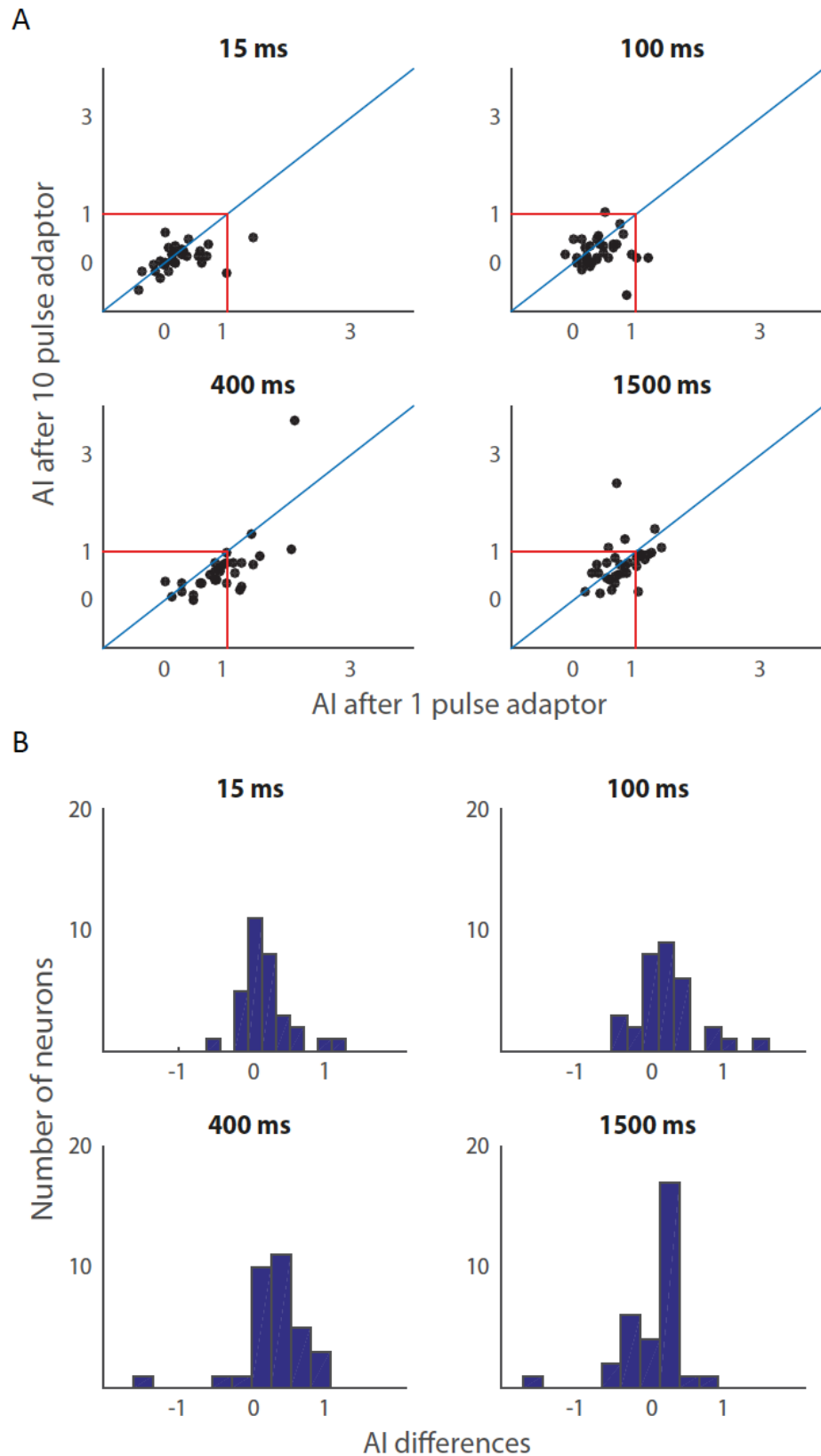


Figure 11. *A*: Scatterplot of Adaptation Index after a ten pulse adaptor plotted against Adaptation Index after a single pulse adaptor. Blue line indicates equality of the two values. Red lines indicate where the value along a particular axis is equal to 1. *B*: Histograms showing differences between Adaptation Indices for single pulse and ten pulse adaptors, one for each of the four adaptor-test separations used in Experiment One.

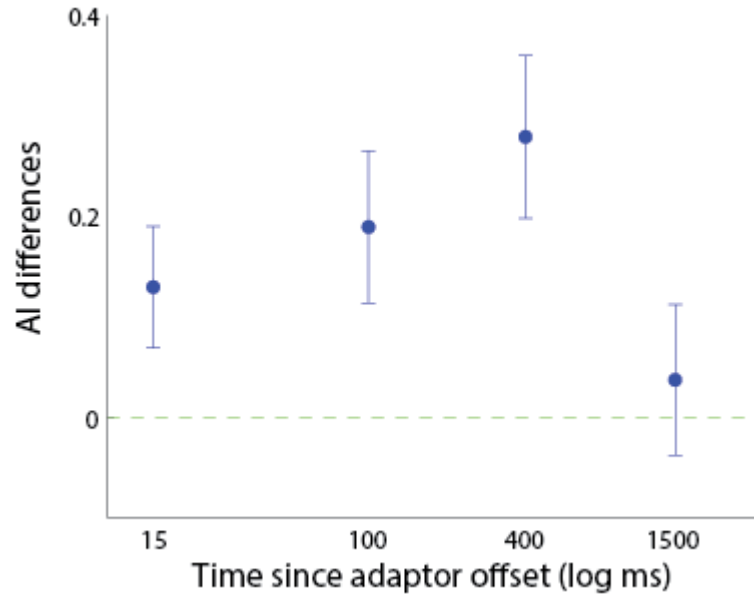


Figure 12. The differences between Adaptation Indices for single pulse and ten pulse adaptors, plotted in Fig. 11 as histograms, are here plotted as means against the time since adaptor offset. Error bars are standard error. The green dotted line is the equity line where the Adaptation Indices are the same regardless of the preceding adaptor's length.

variety of signal detection thresholds. Examining the overlapping histogram distributions of spike counts for both the positive and negative control windows of a sample neuron (Fig. 15 A), it is easy to see how increasing the signal detection threshold would reduce the false alarm rate while also reducing the hit rate. At a signal detection threshold of zero spikes, both the hit rate (percentage of stimulus-present trials identified as such) and the false alarm rate (percentage of stimulus-absent trials misidentified as stimulus-present) would be equal to 1. At the opposite extreme, a signal detection threshold equal to one greater than the highest recorded spike count (that threshold being five spikes in this case) would result in both the hit and false alarm rates being equal to 0. Intermediate thresholds would be expected to produce hit and false alarm rates intermediate between these two extreme case coordinates, as is apparent in a sample plot of hit rate against false alarm rate for all extreme and intermediate detection thresholds, known in signal detection theory as a Receiver Operating Characteristics (ROC) curve (Fig. 15 B). The area under this ROC curve (AUROC) provides a standard measure of discriminability between the positive and negative controls. In Fig. 15 C & E equivalent histogram of stimulus present versus stimulus absent are shown for the 50 ms

window falling 100 ms after the offset of either a one or a ten pulse adaptor, respectively. It is immediately apparent from these histograms that the discriminability between stimulus present and absent conditions has been reduced by the adaptor, as is reflected in the corresponding ROC curves of Fig. 15 D & F in which the areas under the curve are markedly reduced in comparison to Fig. 15 B.

The changes in AUROC over time for stimuli presented after either of the two adaptor conditions are shown in Fig. 16 A. As expected, discriminability is reduced shortly after the adaptor pulses but recovers with time. The population average for such recovery of discriminability shows a similar pattern in Fig. 16 B. Note also the strong resemblance between the recovery time-courses for discriminability shown in Fig. 16 B (for which ANOVA results showed a significant effect of adaptor length, $p = 0.01$) and those shown for normalised response magnitude in Fig. 10 A, indicating a correlation between decreased spike responses and decreased capacity for an observer to discriminate between presence or absence of a test deflection. This decrease in presence/absence discriminability is in line with previous reports finding that adaptation reduces the capacity to detect stimuli similar to the adaptor (Adibi *et al.*, 2013a; Ollerenshaw *et al.*, 2014).

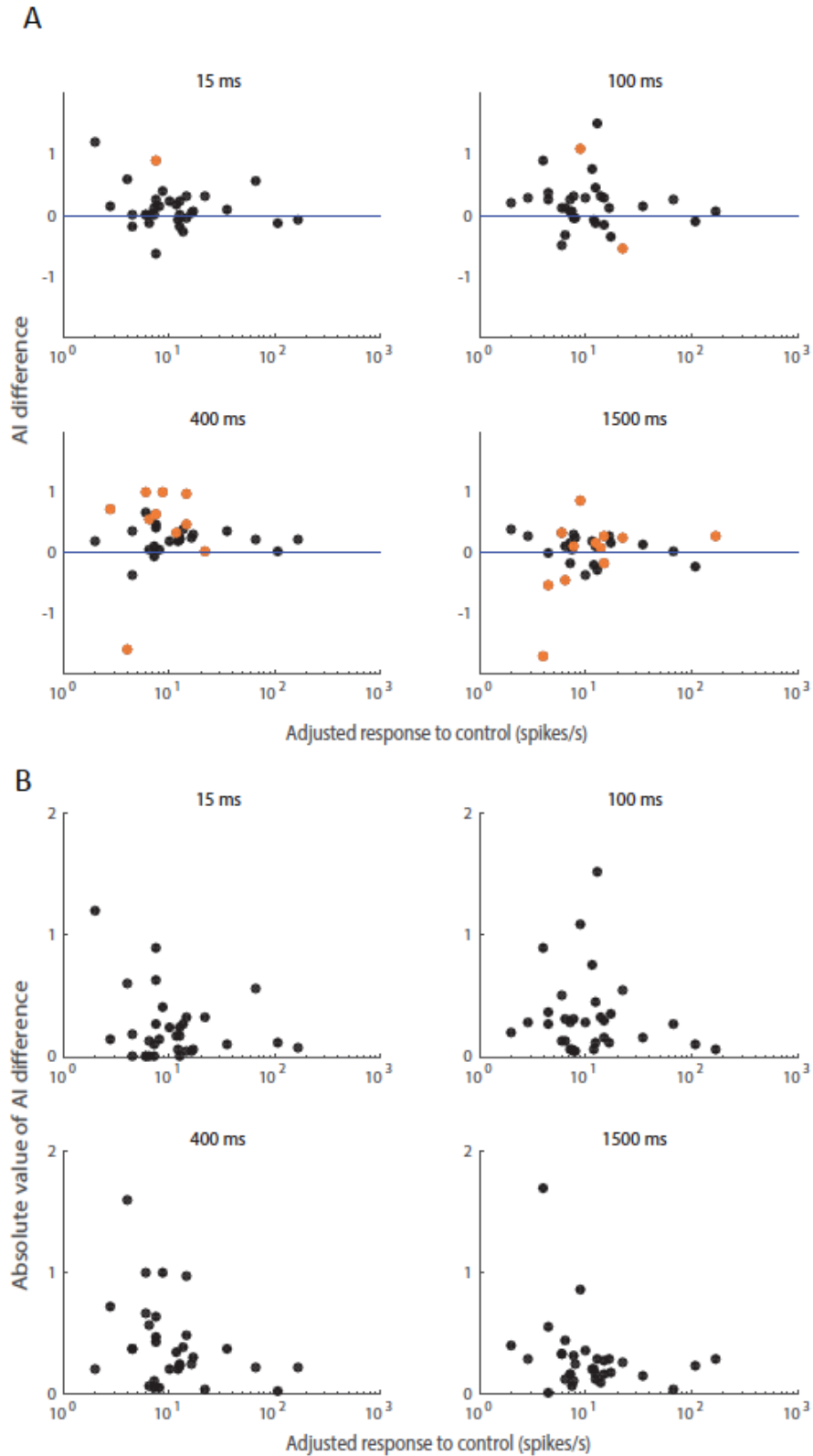


Figure 13. A: Scatterplots showing differences between Adaptation Indices for single pulse and ten pulse adaptors plotted against the background adjusted spike response magnitude for the positive control, one for each of the four adaptor-test separations used in Experiment One. Orange dots indicate cases where the Adaptation Index for either or both conditions was greater than 1. B: Scatterplots similar to those in A, except plotting the absolute value of differences between Adaptation Indices for single pulse and ten pulse adaptors.

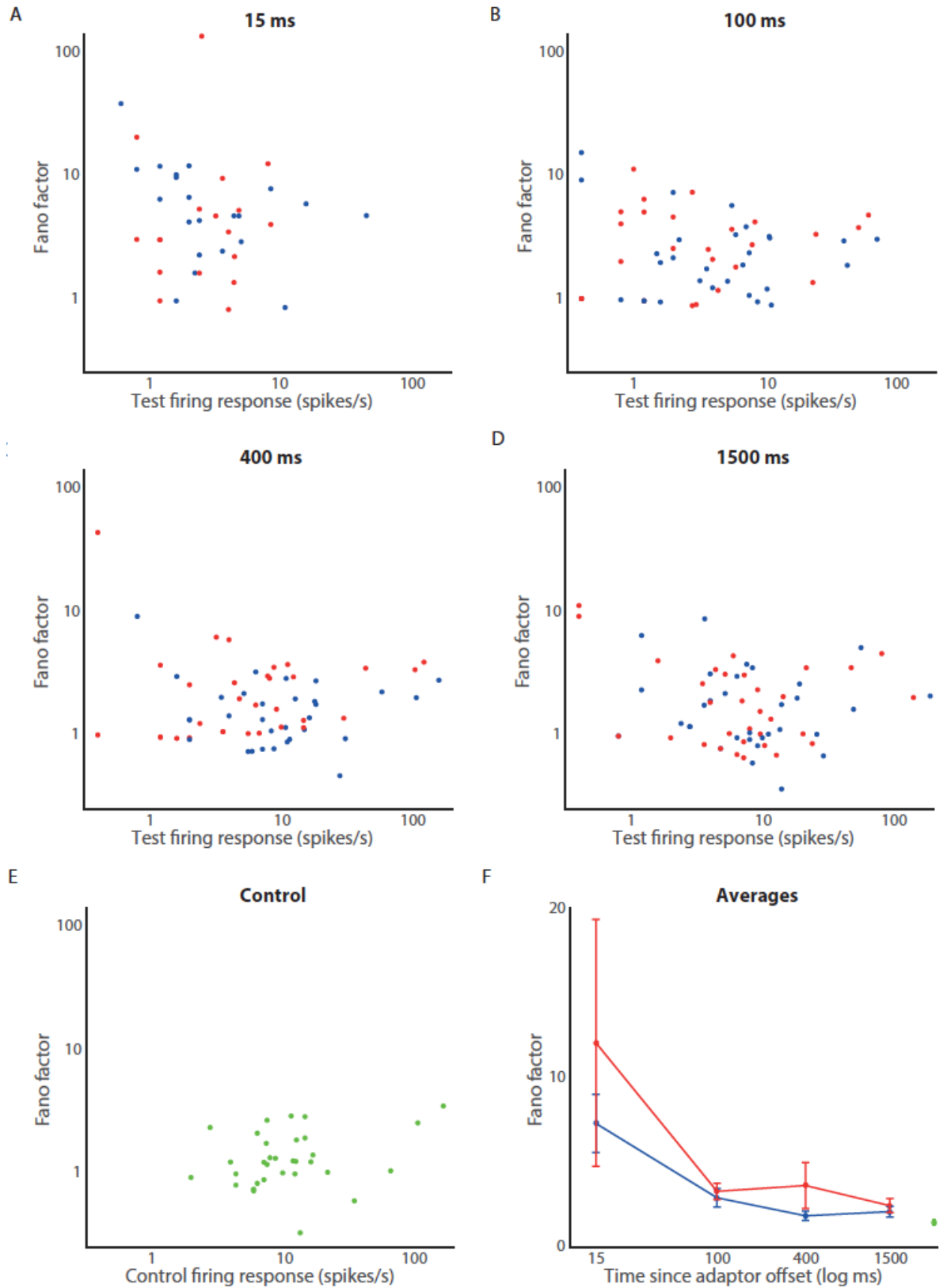


Figure 14. A-E: Fano factors plotted against background-adjusted magnitudes for response to test (A-D) or positive control (E) deflections. In A-D, each neuron has two points plotted, one for a test response after a single pulse adaptor (blue) and the other for a test response after a ten pulse adaptor (red). No point is plotted in the case of an undefined Fano factor value. F: Time-course of decrease in Fano factors for single pulse (blue) and ten pulse (red) adaptor conditions. Error bars are standard error.

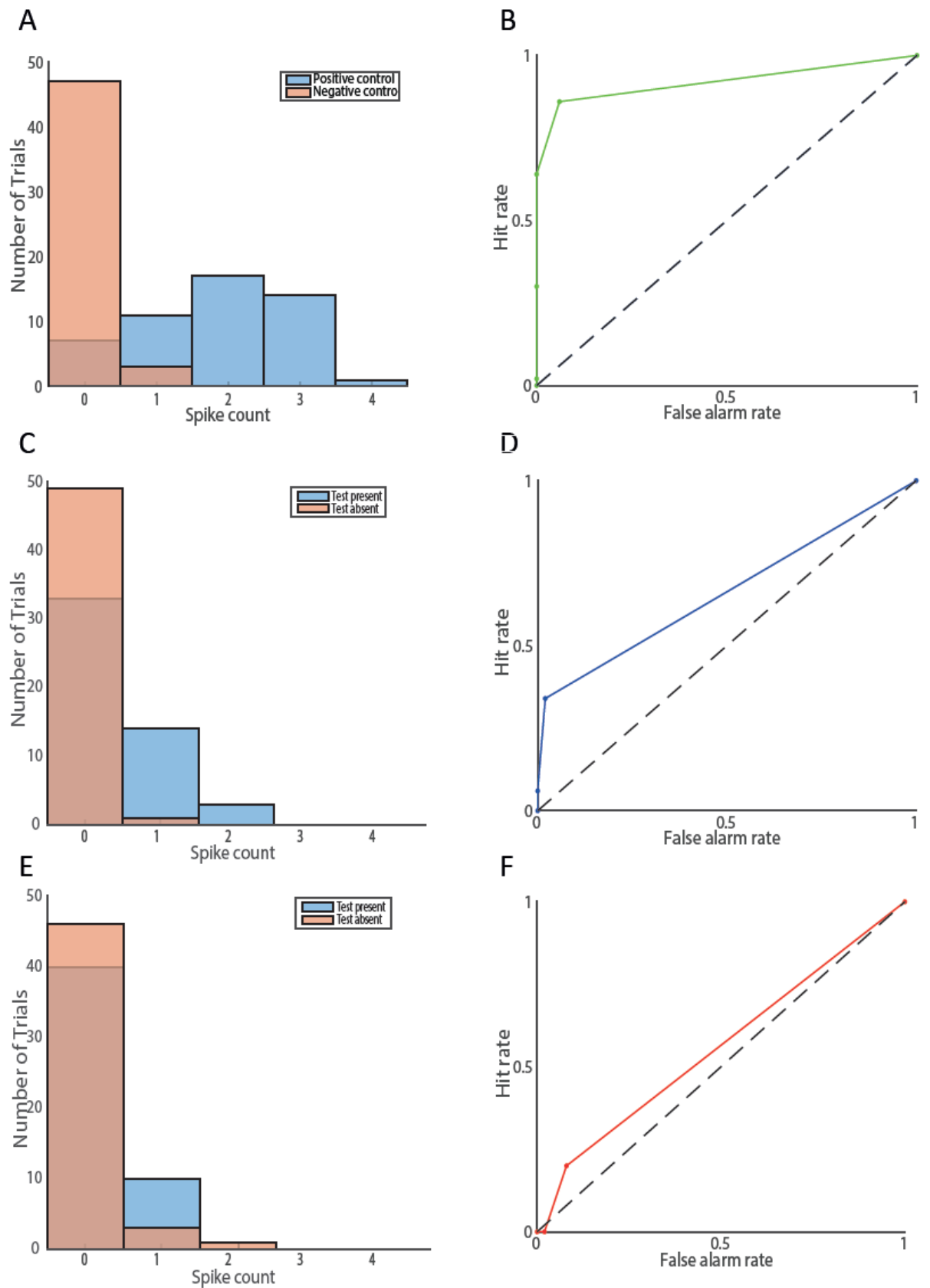


Figure 15. A, C, & E: Histograms showing spike count distribution over 50 trials in both test present (blue) and test absent (orange) conditions for positive control (A), 100 ms after a single pulse adaptor (C), and 100 ms after a ten pulse adaptor (E) conditions. B, D, & F: Receiver operating characteristic curves for the same conditions as in A, C, & E, respectively.

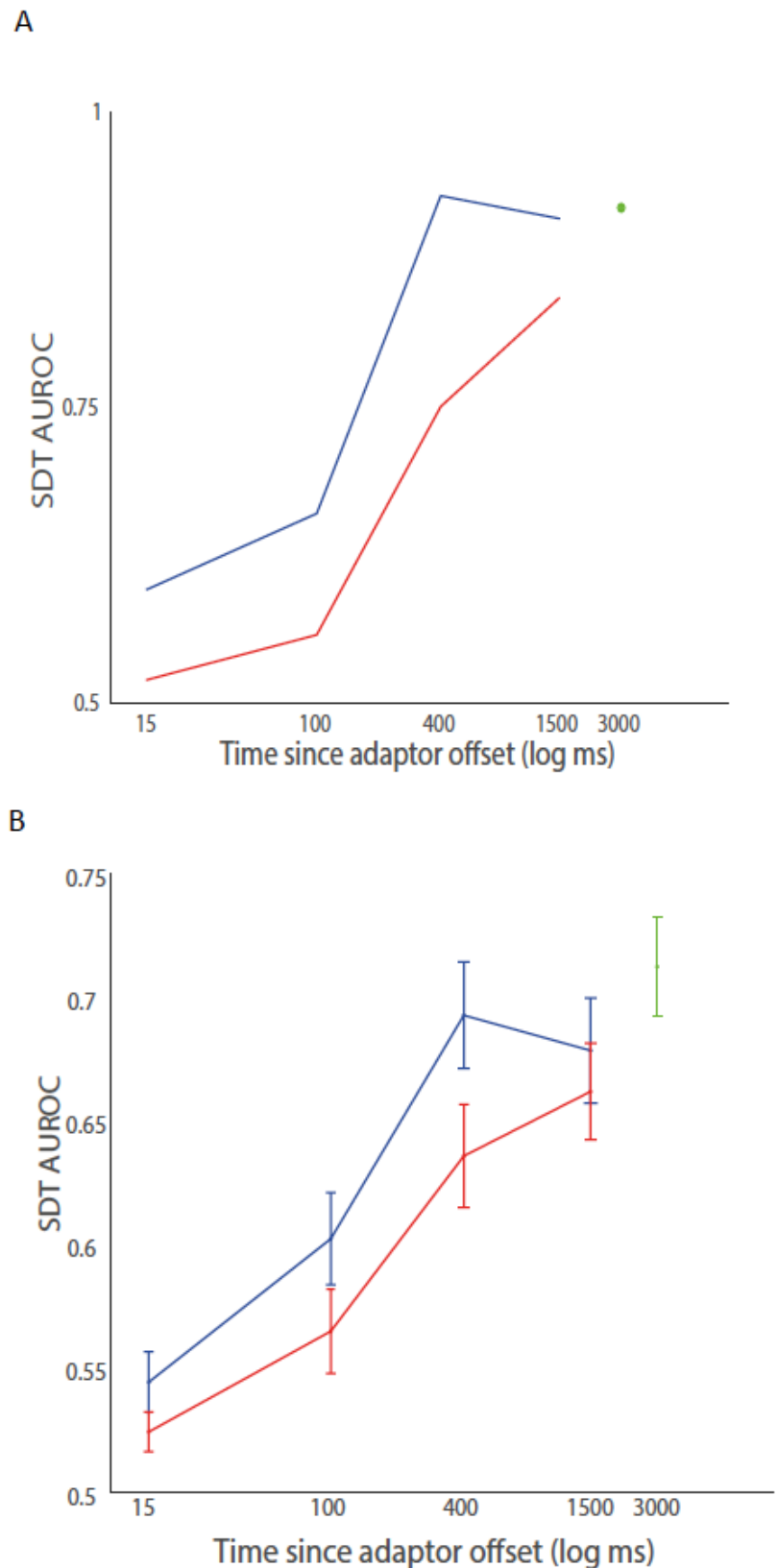


Figure 16. A: Area under the ROC curve (AUROC) recovery time-course plotted for both single pulse (blue) and ten pulse (red) adaptor conditions for the example neuron used in Fig. 15. Positive control AUROC shown in green. B: Population average ($n = 32$ neurons) AUROC recovery time-courses for both single pulse (blue) and ten pulse (red) adaptor conditions. Positive control averages shown in green. Error bars are standard error.

Experiment 2

To obtain a higher resolution understanding of recovery of sensory-evoked activity in the cortical neuron, I next performed experiments investigating test deflection responses at an expanded range of different adaptor-test temporal separations, using only the single pulse adaptor condition as a way of accommodating the greater number of separation conditions. The normalised average recovery course in Experiment One (Fig. 10 A) showed a considerable degree of recovery occurring between 100 and 400 ms, and so a set of adaptor-test separations was chosen that included a high number of temporal separations within this range. Specifically the separations used included one every 25 ms from 25 ms to 400 ms and then one every 200 ms from 400 ms to 1000 ms (Fig. 17 A). Positive, negative, and background firing controls were performed in the same way as in Experiment One (compare Fig. 17 B-D with Fig. 8 A-C). To briefly recap, the positive control was a whisker deflection presented without any recent adaptor deflections, the negative control was a measurement of the background firing rate without any recent deflections, and the background firing control was achieved by presenting an adaptor deflection and then measuring the background firing rate in the absence of any test deflection. The positive and negative controls (i.e. non-adapted controls) were presented after a minimum of 2100 ms of silence. This allowed for detection of both adaptive depression (Fig. 17 B) and adaptive facilitation (Fig. 17 C). Normalisation of test deflection responses was carried out in the same manner as in Experiment One (Fig. 8 D-E), with the background-corrected firing rate at a given separation being divided by the background-corrected control firing rate. An Adaptation Index (Equation 1) below 1 indicates adaptive depression while a value above 1 indicates adaptive facilitation. Two sample Adaptation Index v. temporal separation plots are shown in Fig. 18. The specific neuron from which the raster plots in Fig. 17 B-D are taken is shown in Fig. 18 A, with a clear facilitation of spike responses at 175 ms. The neuron shown in Fig. 18 B has a more expected pattern of recovery from adaptive depression without any facilitation occurring.

Taking the average of normalised responses across the population of 31 barrel cortex neurons (depths ranging from 620 to 2700 μm below the surface, noting that insertions were often made at an angle to the brain surface other than perpendicular) from 13 different rats (Fig. 19 A), it immediately becomes clear that the population average has a sigmoidal recovery behaviour, with a steep rise centred on the range from 100 to 400 ms confirming the observation from Experiment One. Given that studies of synaptic depression in multiple synaptic types in both the central and peripheral nervous system have reported an exponential recovery pattern in EPSP amplitudes (Finlayson and Cyander, 1995; Dittman and Regehr, 1998; Wu and Betz, 1998; Finnerty *et al.*, 1999; Petersen, 2002; Wang and Manis, 2008; Crochet *et al.*, 2011), I hypothesised that the action potential recovery curve should be sigmoidal. My reasoning is that there should be an initial lower plateau in which EPSPs did not have sufficient amplitude to reach action potential threshold, a later upper plateau in which EPSPs had recovered to their non-adapted state, and between them a central region in which partially recovered EPSPs may, due to trial-trial variability in EPSP magnitude, exceed the action potential threshold in some trials but not in others, resulting in a firing probability that is midway between the adapted and non-adapted states. Background fluctuations in membrane potential are unlikely to assist an EPSP in reaching the firing threshold, as EPSP-evoked membrane potential changes are negatively correlated with background depolarisations, leaving the final membrane potential resulting from an EPSP unaffected by background membrane potential fluctuations (Crochet *et al.*, 2011) or possibly even further from the action potential threshold than would have been the case had the neuron not been in a state of background depolarisation (Petersen *et al.*, 2003). Based on how readily a sigmoid (Equation 2) can be fitted to the data in Fig. 19 A, it appears that the prediction of a sigmoidal recovery curve is confirmed. These data support the predictions made from the short-term synaptic dynamics hypothesis, and also match findings in the primary auditory cortex (Eggermont, 2000). Worth noting is the fact that such a sigmoid recovery function emerges despite a considerable diversity of individual adaptation recovery time-courses (Fig. 19 B).

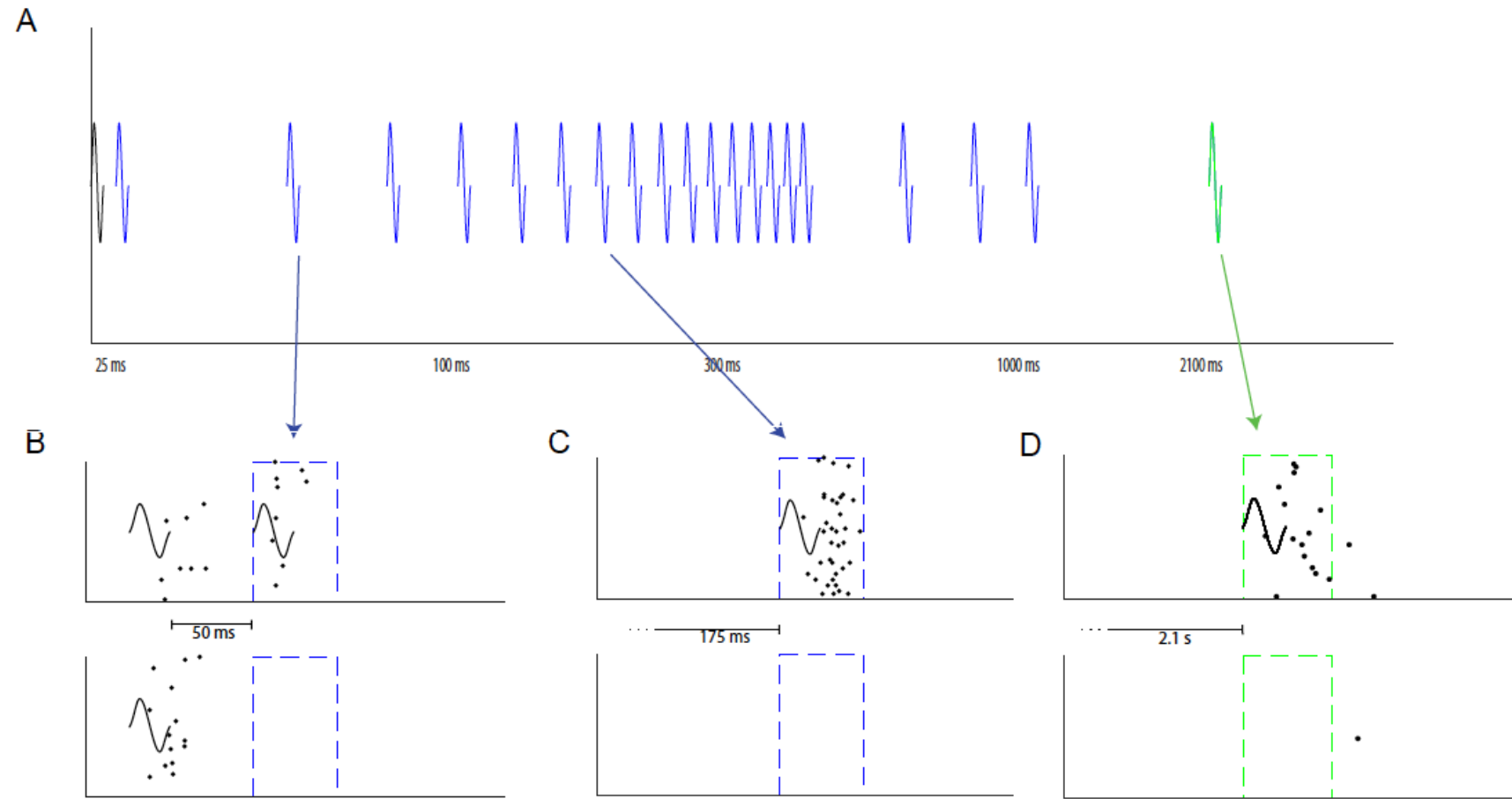


Figure 17. *A:* General schematic for Experiment Two protocol, with single pulse adaptor in black, candidate test pulses shown in blue, and positive control pulse shown in green. Superimposed sinusoids are scaled on the x-axis to faithfully represent the time-course of piezo deflections. *B-D:* Quantification windows for test response (top) and background correction (bottom) are indicated in blue boxes for candidate test separations (*B* & *C*) and in green boxes for the positive control (*D*).

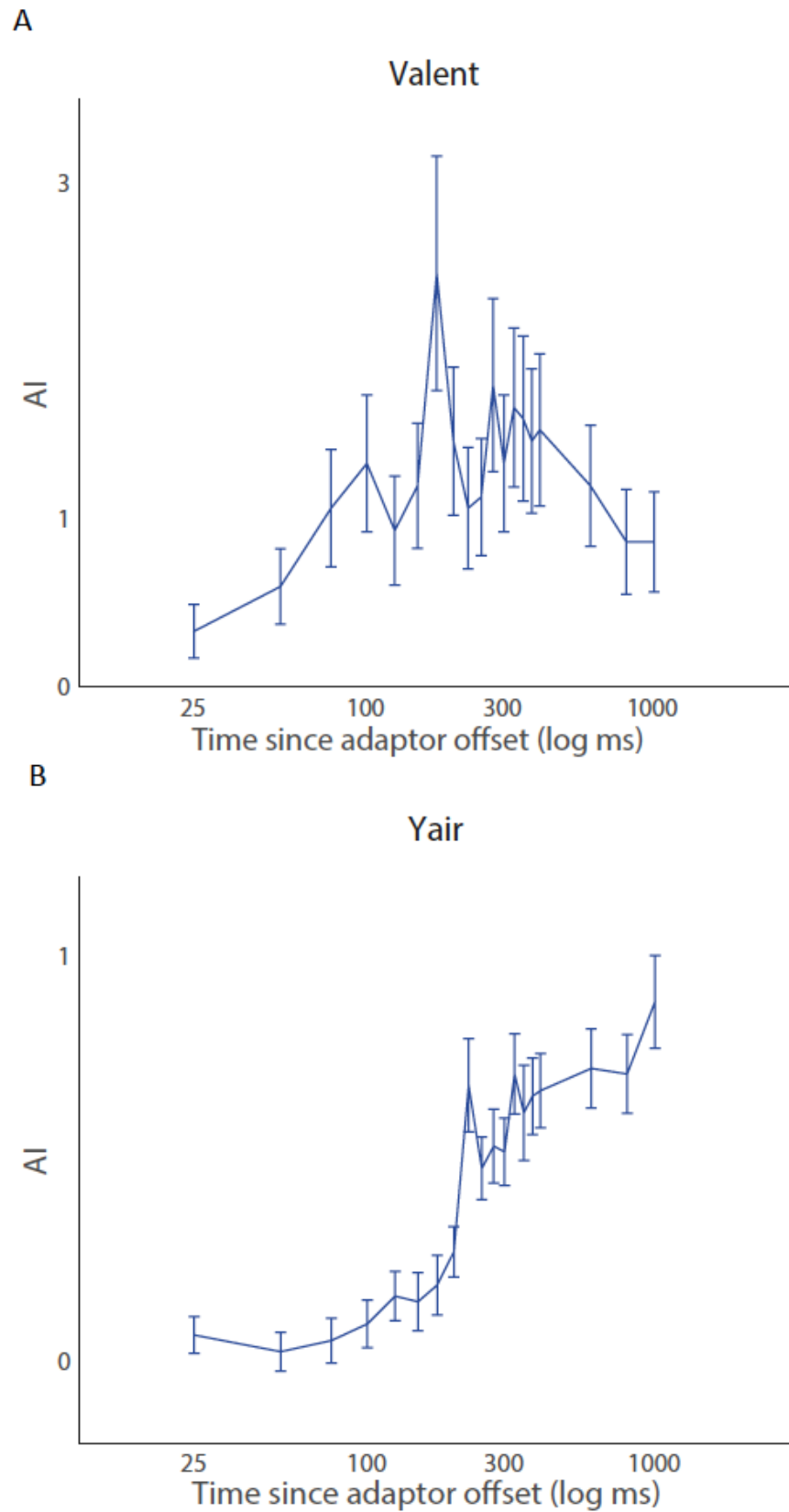


Figure 18. Adaptation recovery time-courses for two example neurons, the neuron in A being the one for which example raster plots were provided in Fig. 17 B-D. Error bars are standard error.

Previous literature on adaptation has reported that neuronal responses in adapted states have higher trial-to-trial variability than in an unadapted state (Adibi *et al.*, 2013a, 2013b), a phenomenon that manifested itself in Experiment One (Fig. 14 F). To investigate whether this was also true for Experiment Two, I calculated Fano factors (Equation 3) for the paired-pulse experiments. In performing the analysis for the data for Experiment Two (Fig. 20 A), much the same result was observed, with a negative correlation between Fano factors and the adaptor-test temporal separations (Pearson's $R = -0.6487$).

Given the decrease in response magnitude (Fig. 19 A) and the increase in trial-to-trial response variability (Fig. 20 A), the question of an observer's capacity to discriminate between the presence or absence of a test pulse is immediately raised. Signal detection theory was applied to the data from Experiment Two in the same manner as for Experiment One (Fig. 15 & Fig. 16), producing an expected result of discriminability, as measured by area under an ROC curve, being reduced after an adaptor pulse and gradually rising over the next second to a value equal to the value for the non-adapted control (Fig. 20 B) with a rapid rise within the 100 to 400 ms range.

Given the diversity of adaptation across neurons revealed in Fig. 19 B, we next examined the potential sources of the heterogeneity. However, no correlations were found between neurons' behaviours and their background firing rate, non-adapted test stimulus response, or depth (Fig. 21 B-D).

One of the original goals of this project was to explore correlations between the morphology of individual neurons and their adaptation behaviours. Though histological recovery of morphology is a capability of the juxtacellular method, this was only achieved for a few neurons in the latter stages of Experiment Two. At present there are ten such neurons for this database, and they are visualised in Fig. 22. This sample is mainly composed of neurons from L5, and some of them showed intriguing individual adaptation behaviours in Experiment Two. One of these L5 neurons, referred to as Sadaf, displayed facilitation at two

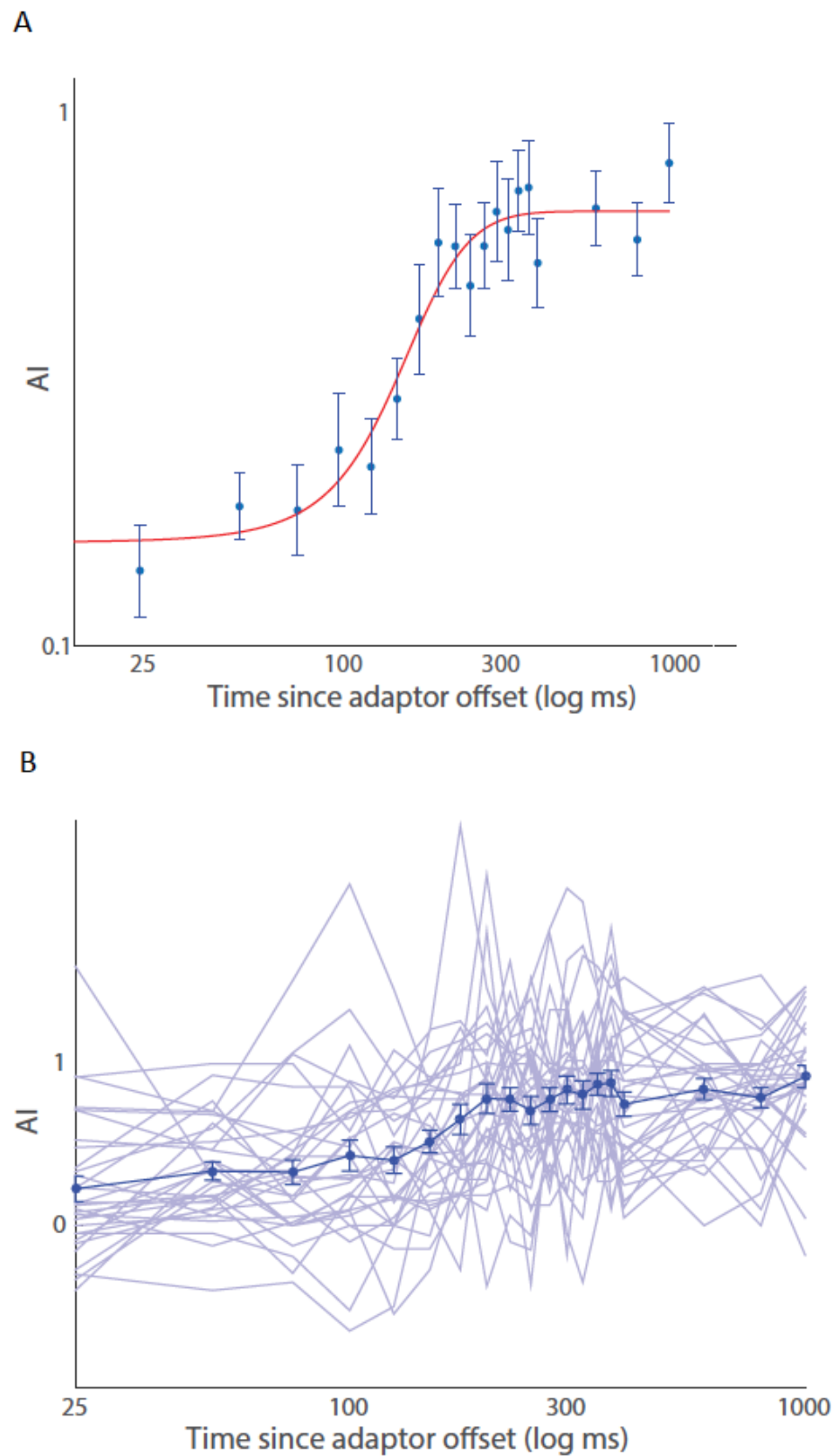


Figure 19. *A:* Averaged Adaptation Indices across population ($n = 31$ neurons). The sigmoid curve-fit result (Equation 2) is shown in red. Error bars are standard error. *B:* Population averages (opaque blue) plotted alongside adaptation recovery time-courses for individual neurons (transparent blue).

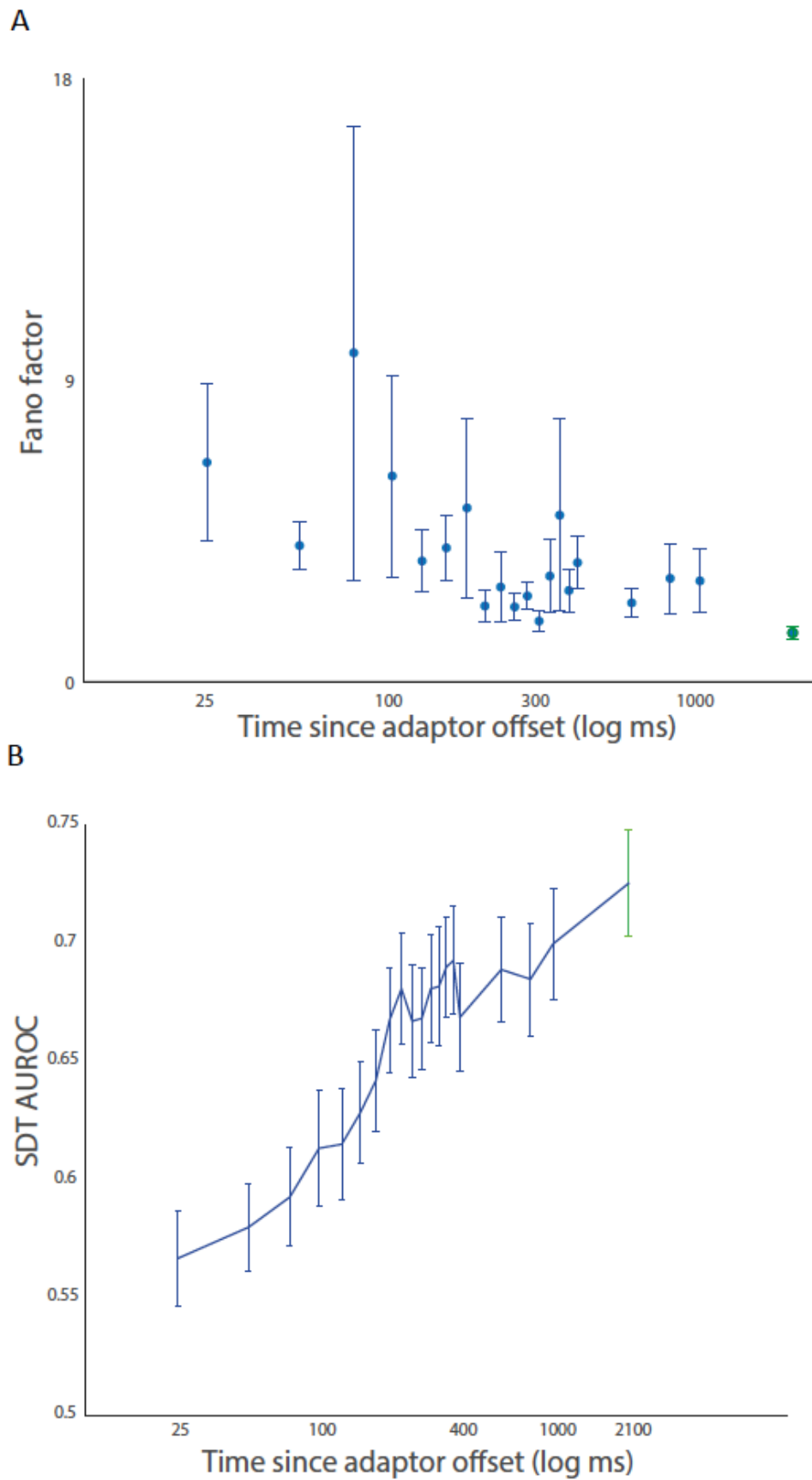


Figure 20. *A:* Time-course of decrease in Fano factors. Error bars are standard error. *B:* Time-course for AUROC increase.

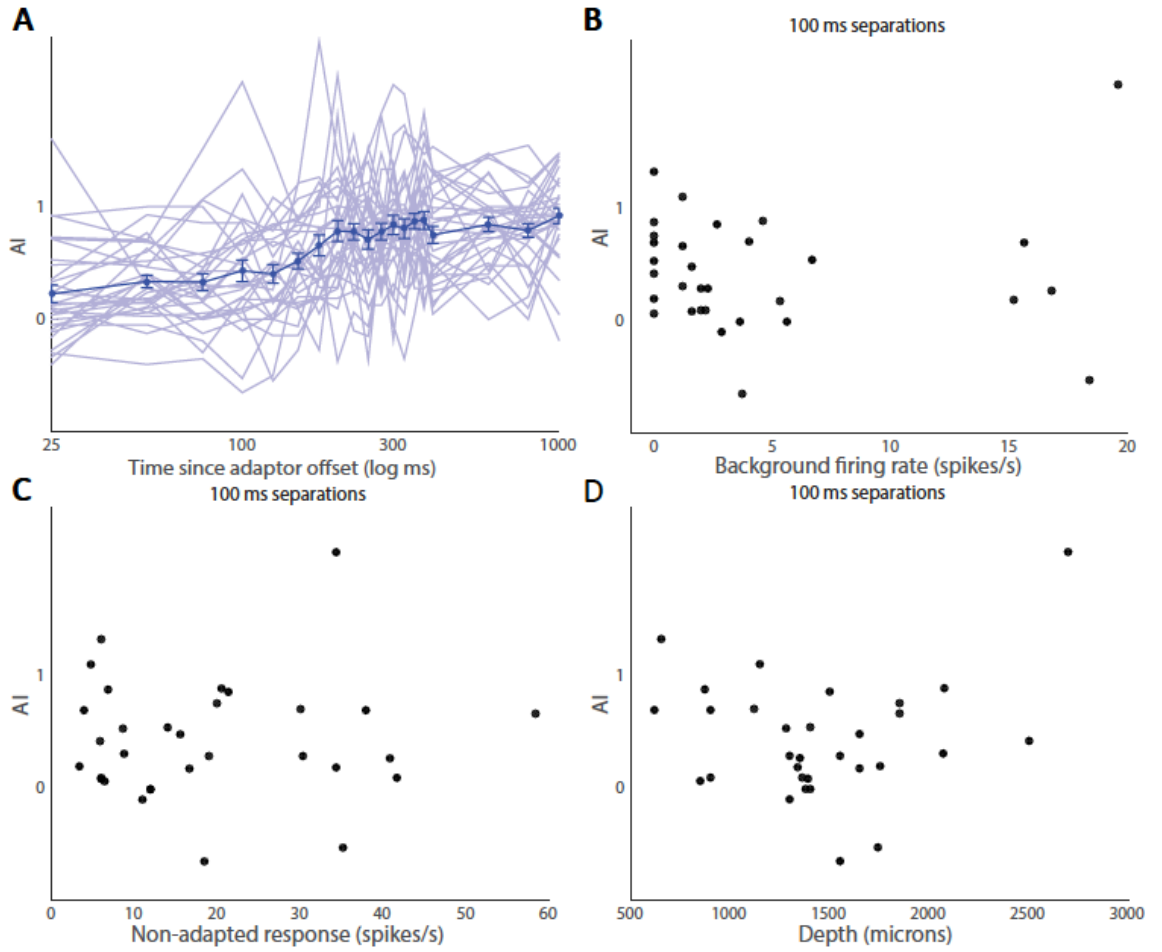


Figure 21. A: Population averages (opaque blue) plotted alongside adaptation recovery time-courses for individual neurons (transparent blue). B, C, & D: Adaptation indices for individual neurons at 100 ms adaptor offset-test onset separation, plotted against background firing rate, non-adapted test response, and depth, respectively.

adaptor-test separations (Fig. 23 A). Another L5 neuron, referred to as Tadg, did not exhibit the same strong facilitation of action potentials, but did show a surprising reversal of recovery that had been achieved by 300 ms, suggesting that shortly before 300 ms some synapses onto it may have been facilitated while others were still depressed (Fig. 23 B). Such facilitation profile is consistent with literature reports documenting facilitation of post-synaptic potentials in L5 recurrent circuitry (Markram and Tsodyks, 1996; Markram *et al.*, 1997).

A curious case of sudden recovery from adaptation can be seen in neuron Wes (Fig. 23 C), which appears to be an L4 spiny stellate neuron. The abrupt recovery at 1000 ms is likely due to the fact that this neuron's AP responses were sparse even in the unadapted case, and the discrete nature of action potential activity exaggerates the impact of any omitted or

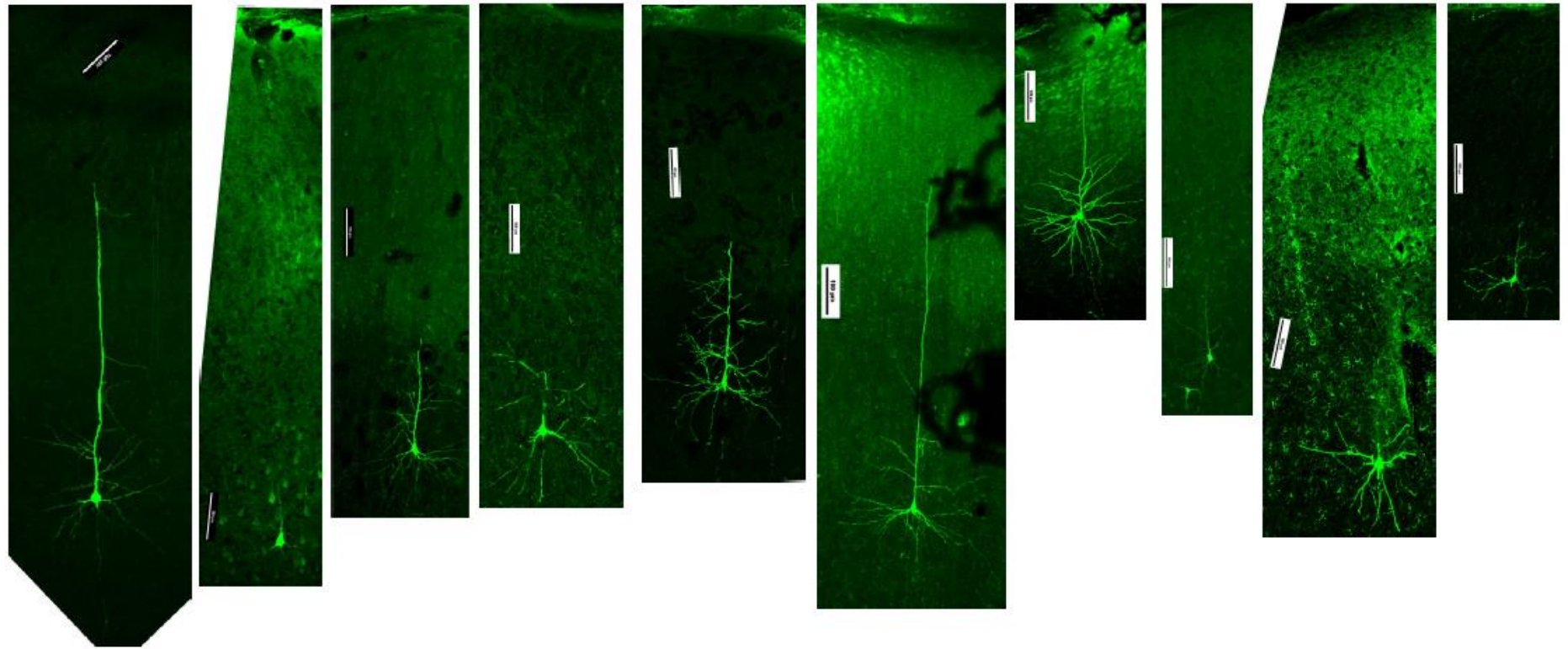


Figure 22. Ten histologically recovered neurons. Each neuron is accompanied by a 100 μm scale bar.

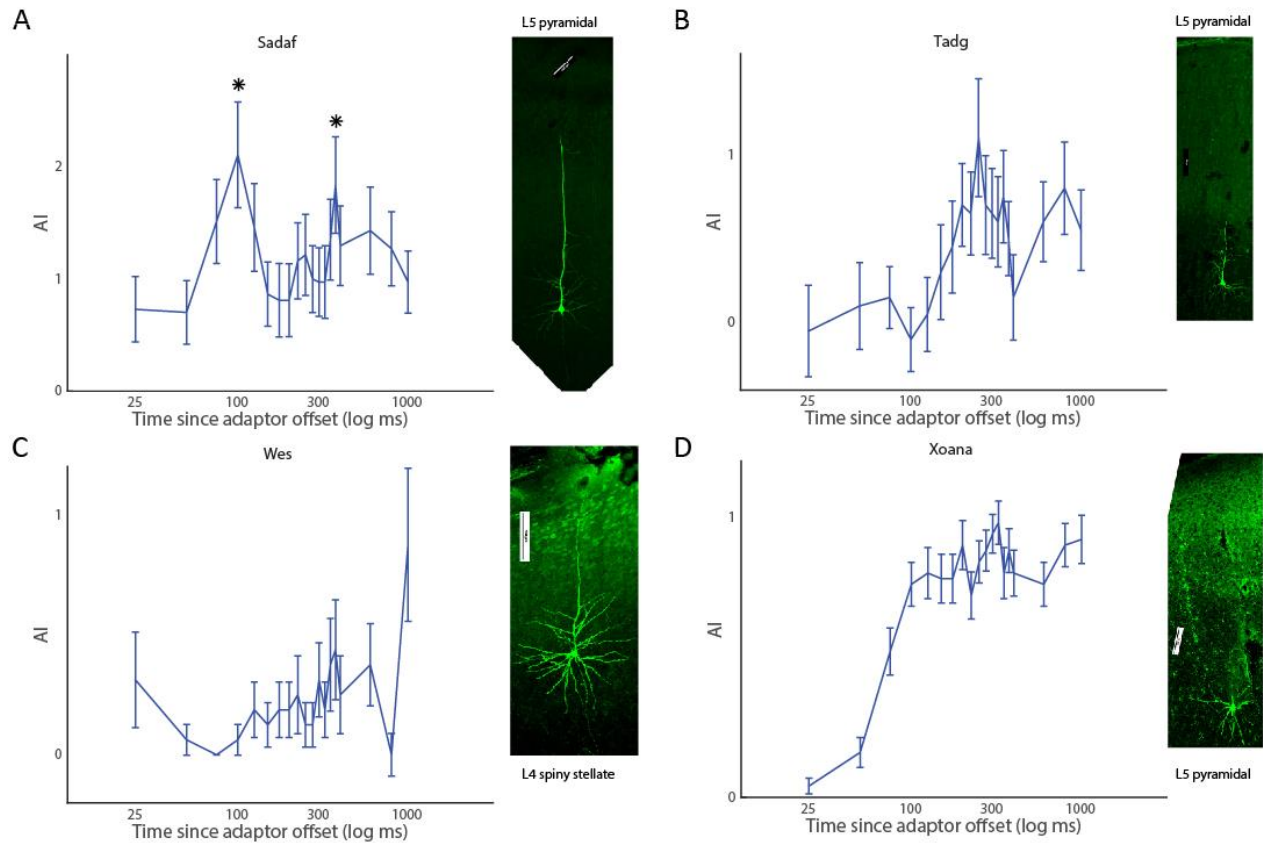


Figure 23. A-D: Adaptation recovery time-course plots for four example neurons, accompanied by histological recoveries.

additional spike in such conditions. A more thorough investigation of L4 adaptation time-courses would be necessary to determine whether such step-wise recovery time-courses are common.

As a final case-study, neuron Xoana (Fig. 23 D) was another L5 neuron which returned a recovery function with a shape closely matching what one would likely predict *a priori*, with early depression of responses, rapid recovery, and thereafter response magnitudes similar to the non-adapted state. The contrast between this form of behaviour and that exhibited by neuron Sadaf serves as an example of diversity of intralaminar neuronal behaviour. In summary, these results demonstrate that, while adaptation of neuronal responses to stimuli is a ubiquitous phenomenon within the barrel cortex, its exact nature and time-course will vary widely between individual neurons, with correlations between neuronal identities and adaptation behaviours that have yet to be fully elucidated.

Discussion and Future Directions

The two experiments described in this study found adaptive depression of cortical neuron responses following a history of prior stimulation (Fig. 10 A & 15 A). It was demonstrated that the time-course of recovery from this depression was dependent on the duration of the adaptor stimulus (Fig. 10 A), consistent with previous reports on the effect of adaptor frequency as an alternative adaptor intensity variable (Chung *et al.*, 2002; Khatri *et al.*, 2004). I found that adaptation increased trial-to-trial variability of responses to stimuli (Fig. 14 F & Fig. 20 A), consistent with earlier reports (Seriès *et al.*, 2009; Adibi *et al.*, 2013a, 2013b). Adibi *et al.* (2013a) found that for neurons in the non-adapted state, Fano factors decreased as the intensity of whisker stimulus increased. They were thus able to explain increased trial-to-trial variability in adapted neurons as arising from an increase in the stimulus intensity necessary to achieve a decrease in Fano factors. Seriès *et al.* (2009) also linked changes in Fano factor in adapted neurons to elevation of thresholds. Signal detection theory revealed that adaptation reduced the detectability of stimuli with characteristics similar to the adaptor with a time-course for recovery dependent on adaptor duration (Fig. 16 B & Fig. 20 B), consistent with previous findings in the literature (Adibi *et al.*, 2013a; Ollerenshaw *et al.*, 2014).

The computational justification for this decrease in detectability of adaptor-like stimuli has been posited to be an increase in the detectability of stimuli that are substantially different from the adaptor stimulus (Wang *et al.*, 2010; Musall *et al.*, 2014; Ollerenshaw *et al.*, 2014). The reduced ability to discriminate between presence or absence of a repetitive stimulus, demonstrated through signal detection theory, is consistent with the hypothesis of adaptation impairing detection of familiar stimuli in favour of enhanced detection of novel stimuli (Ollerenshaw *et al.*, 2014) and the previous finding that adaptation shifts neuronal response thresholds to match the average environmental stimulus intensity (Adibi *et al.*, 2013a).

Although EPSPs are known to recover according to an exponential function (Finlayson and Cyander, 1995; Dittman and Regehr, 1998; Wu and Betz, 1998; Finnerty *et al.*, 1999; Wang and Manis, 2008; Crochet *et al.*, 2011), this investigation found that recovery of action potential responses followed a sigmoidal function. This is in contrast to the results of a similar experiment by Chung *et al.* (2002) who reported an exponential recovery, but it should be noted that the most brief adaptor-test separation they used was 250 ms, whereas my Experiment Two involved separations as brief as 25 ms. One of the key findings of this study is that the midpoint of the sigmoid, the temporal region with the greatest rate of cortical response recovery from adaptation, lies in the range of 100 and 400 ms for recovery from a single-pulse deflection. This finding is consistent with intracellular studies of EPSP recovery in the barrel cortex, such as the observation from Crochet *et al.* that EPSP's in L2/3 pyramidal cells had reached half-recovery by 100 ms (see Fig. 8E in Crochet *et al.*, 2011) and reports that full recovery of EPSPs can be achieved at around 500 ms in L2/3 pyramidal cells (Finnerty *et al.*, 1999) and L4 excitatory neurons (Petersen, 2002). It is also consistent with the timescales for adaptation reported by Maravall *et al.* (2007) for induction of adaptation, which may hold interesting clues as to shared mechanisms of induction of and recovery from adaptation. Exponential EPSP recovery functions with similar timescales (hundreds of milliseconds) have been reported in the rat visual cortex (Abbott *et al.*, 1997; Veralá *et al.*, 1997), so I predict that recordings of action potential recovery in paired pulse paradigms applied to that modality would return a similar sigmoidal recovery function to what I have found in the somatosensory cortex. The time-course observed in Experiment Two is also consistent with a report from Khatri *et al.* (2004) whose study of whisker deflection trains found virtually no adaptation in response to a 1 Hz stimulation frequency but did observe weak adaptation at a 4 Hz stimulation frequency.

This finding on recovery timescales is also consistent with the hypothesis of adaptation being induced during periods of attention (Castro-Alamancos, 2004), as it

would result in cortical neurons remaining in a persistent adapted state between object contacts if a rat were whisking an object at typical whisker protraction frequency of 10 Hz (Carvell and Simons, 1990; Berg and Kleinfeld, 2003). Temporal regions of partial response probability could additionally serve as an explanatory factor in the known desynchronisation of neuronal stimulus responses in the adapted cortex (Khatri and Simons, 2007; Khatri *et al.*, 2009), though the plot of Fano factors against adaptor-test temporal separation does not show the elevation of trial-to-trial variability in the 100 to 400 ms range that would be expected as a consequence.

Though averaging of individual neurons gathered in Experiments One and Two produced results that were unsurprising, this averaging is flawed as it serves as a homogenisation of a population that is fundamentally heterogenised on laminar, morphological, neurochemical, and functional characteristics (Feldmeyer *et al.*, 2013). Some hint of this heterogeneity could be seen in the diversity of adaptation time-courses for individual neurons (Fig. 10 B & 15 B), consistent with literature reports that time scales of adaptation in individual neurons are non-static (Lundstrom *et al.*, 2008) and that individual thalamocortical synapses can display a range of adaptation ratios (Díaz-Quesada *et al.*, 2014). In examining the diversity of adaptation ratios at the 100 ms mark in Fig. 19 B, where the variance was the highest, no correlation could be found between neurons' behaviours and their background firing rate, non-adapted test stimulus response, or depth (Fig. 21 B-D).

Several reports in the literature exist which serve to demonstrate diversity of adaptation behaviours. The importance of correlating adaptation behaviours to individual neuronal identities was demonstrated in a paper by Ahissar *et al.* (2000), who found that L4 barrel cortex neurons exhibited adaptation behaviours similar to the lemniscal pathway VPM neurons that excite them, whereas L5A neurons behaved more like the paralemniscal pathway POm neurons from which they receive direct excitation. Furthermore, in a study (Derdikman *et al.*, 2006) of touch-dependent adaptation in

anaesthetised rats, laminar differences in adaptation behaviours were observed in the somatosensory cortex. Recording neurons extracellularly while applying electrically induced artificial whisking either in air or against an object, they observed depression of neuronal responses in L2/3 but facilitation in L5A. In comparing adaptation to constant rate deflection trains and to deflection trains with irregular intervals (Maravall and Diamond, 2014), it has been observed that excitatory cortical neurons adapt more strongly to deflections at a constant rate while inhibitory neurons do the opposite (Lak *et al.*, 2008, 2010). A study of local field potentials in rat primary auditory cortex found that stimulus-specific adaptation was much stronger in L5 than in the main thalamorecipient layers L3 and L4 (Szymanski *et al.*, 2009). A study of the macaque primary visual cortex found that rapid adaptation increases neuronal synchronisation specifically in the supragranular output layers (Hansen and Dragoi, 2011). Similarly, a study of macaque primary auditory cortex found the most pronounced adaptation effects in supragranular layers (Javitt *et al.*, 1994).

Further diversity of adaptation behaviours can be found in a paper examining thalamic projections to cortical interneurons, which found that synapses onto PV-expressing interneurons of L4 and L5 exhibited adaptive depression whilst SOM-expressing interneurons of L3 exhibited facilitation (Tan *et al.*, 2008). Similarly, projections from L4 spiny stellate cells to various L2/3 interneuron classes show adaptive depression in some cases but facilitation in others (Helmstaedter *et al.*, 2008). The same is true of L2/3 pyramidal projections onto various L2/3 interneuron varieties (Reyes *et al.*, 1998; Rozov *et al.*, 2001; Holmgren *et al.*, 2003; Kaiser *et al.*, 2004; Kapfer *et al.*, 2007; Faselow *et al.*, 2008; Pala and Petersen, 2015). Projections between L2/3 pyramidal cells have been documented exhibiting both depression (Finnerty *et al.*, 1999; Holmgren *et al.*, 2003; Feldmeyer, *et al.*, 2006; Kapfer *et al.*, 2007) and facilitation (Gil *et al.*, 1997; Holmgren *et al.*, 2003). Such diversity of behaviours in the cortex is to be expected when one considers that it acts as a station of convergence for different neural pathways

employing different coding schemes (Ahissar *et al.*, 2001) and that inhibitory circuitry within the cortex displays marked differences in laminar organisation (Bodor *et al.*, 2005). Diversity of individual neuron adaptation patterns has also been observed subcortically, with considerable variance observed in the VPM (Maravall *et al.*, 2013).

Taken together, these results indicate that while cross-population averages return results that are expected based on the literature, an exploration of the behaviours of different cell types must be conducted for better understanding of adaptation effects in the cortex. It is also worth noting that the population under consideration was composed of neurons that responded robustly to principal whisker stimulation, which literature reports on sparse coding (Kerr *et al.*, 2007; Jadhav *et al.*, 2009; Wolfe *et al.*, 2010) inform us are a minority of the neurons in the relevant barrel. It is therefore necessary to explore adaptation using population recording techniques in order to understand how adaptation is affecting those neurons that do not robustly respond to whisker deflection in the non-adapted state.

A critical future direction for studies of this type will be to adequately capture information as to the identities of individual neurons recorded from, so that exploration can be made of correlations between adaptation behaviours and the functional roles of neurons. In this study this was only achieved for ten neurons, due in part to my own perhaps overly cautious approach of perfecting the methods for establishing and holding contact with neurons before attempting to master the nanostimulation-electrophoresis procedure for introducing the tracer compound. In retrospect, the more prudent use of opportunities would have been to gain what experience was possible in the electrophoresis procedure even if other aspects of the experiment had not yet been fully mastered. Any proper understanding of cortical adaptation patterns will require a description of how the functional roles of the different cortical layers factor into the adaptation behaviours of the neurons found within them.

In order to better understand how the stimulation history and spiking history of a neuron predict its future spiking and stimulus response behaviours, I have entered into collaboration with Dr. Hossein Vahabi, a computational neuroscientist who is, as of the time of this writing, working to apply a generalised linear model to the data collected in Experiments 1 and 2. Generalised linear models have been successfully applied to the task of modelling stimulus response characteristics of trigeminal ganglion neurons of the whisker pathway (Bale *et al.*, 2013; Campagner *et al.*, 2016). They have also been applied to modelling and decoding population activity of the motor cortex, which may have significant applications in the task of constructing brain-machine interface technologies for assisting the physically disabled (Lawhern *et al.*, 2010). A GLM model has also been successfully applied to characterising spectrotemporal tuning of neuronal populations in the auditory midbrain of zebra finches (Calabrese *et al.*, 2011). Past work in the barrel cortex has applied GLM to modelling the effects of whisker trimming on EPSP amplitudes in L2/3 pyramidal neurons (Cheetham *et al.*, 2007).

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