Interneuron Networks and Cortical Dynamics: Emulated Whisking Drives SOM Interneurons in the Ketamine Anesthetized Mouse SI Neocortex

By

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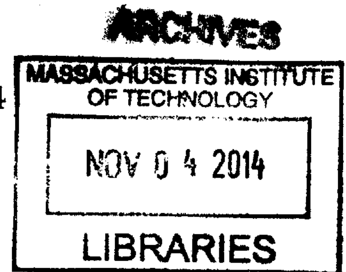

Submitted to the Department of Brain & Cognitive Sciences in Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

In the core of this thesis I test and confirm the hypothesis that separate classes of interneurons respond differentially to sensory stimulation independent of volitional or other top-down control on the part of the animal. I also test and confirm the hypothesis that, based only on bottom-up sensory stimulation the activity of two major classes of interneurons (adapting Parvalbumin positive and facilitating Somatostatin positive interneurons) predominates during different phases of what corresponds to natural sensing cycles in a behaving rodent. These questions are addressed using an *in vivo* mouse model with intrinsically fluorescent, but differentiable, interneuron populations combined with 2-photon imaging, Ca^{2+}-sensitive dyes. Anesthesia and electrical control of facial muscles allowed for naturalistic stimulation without the confounds presented by volitional whisking and unknown top-down or behavioral states. Additional chapters in this thesis focus on ancillary work related to computational modeling of neural systems and systems' level perspectives on maturation and disease.

Thesis Supervisor: Christopher I. Moore

Title: Associate Professor of Neuroscience, Brown University

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Chapter I

Introduction

I.1 Background & Literature

The perceptual demands placed on an animal vary as a function of its changing environment, behavioral goals, and sensory sampling strategy. An efficient internal representation of the environment should match these perceptual demands, giving rise to a dynamic coding strategy. Consistent with this dynamic sensory coding hypothesis, sensory-evoked cortical activity changes with sensory context as a function of the pattern of sensory input, the state of the cortex, and the active sensing goals of the animal. These dynamics have been documented across species, including rats [Moore, *et al.* 1999; Fanselow & Nicolelis 1999; More 2004; Kleinfeld, *et al.* 2006; Ritt, *et al.* 2008], monkeys [Fries, *et al.* 2001; Dragoi, *et al.* 2002; Ray, *et al.* 2008], and humans [Zeki, *et al.* 1991; Keil, *et al.* 1999; Serences, *et al.* 2005; Shibata, *et al.* 2008].

Understanding how different neuron classes contribute to processing during different sensory regimes - especially those under active control - is key to understanding sensory coding and sensory network dynamics. The identification of distinct dynamics in distinct classes of neurons *in vivo* had received little attention until recently. This lack of attention resulted from the fact that most model systems (e.g., monkeys, humans, and rats) do not allow us to know the activity and identity of populations of cells in *in vivo* preparations.

I.2 Concentration of Diversity in the Interneurons

The study of interneurons has become one of the most promising frontiers in neuroscience and may provide understanding of the regulatory backbone of cortical processing. Unlike the relatively large pyramidal cells that make up more than 80% of cortical neurons [Rudy, *et al.* 2010], establish long range connections across brain areas, and almost exclusively account for the release of neurotransmitters with direct excitatory effects, interneurons are smaller and make up most of the remaining 20% of cortical neurons [Nunez, *et al.* 1993; Cherubini & Conti 2001; Krimer & Goldman-Rakic 2001], display almost exclusively local connections [Rudy, *et al.* 2010], and almost exclusively account for the of release neurotransmitters with directly inhibitory effects [Rudy, *et al.*

2010]. Additionally, pyramidal cells possess "spiny" dendrites [Parnavelas, *et al.* 1977; Peters & Kara 1985; Dori, *et al.* 1989; Dori, *et al.* 1992], whereas interneurons provide direct excitatory input to one another almost exclusively by means of passive direct electrical coupling [Gibson, *et al.* 1999; Beirlein, *et al.* 2003; Rudy, *et al.* 2010]. Due to the presumptive passive and relatively linear nature it naively suggests a group of neurons that are little more than, at best, filtered and averaged relays of the "dominant" and driving pyramidal neuron population. The above comparisons, combined with the relative difficulty of recording from a physically smaller and less populous class of neurons with undirected electrodes and the lack of a theoretical framework like Hebbian plasticity explaining inhibitory chemical synapse dynamics, make it easy to understand why interneurons were historically *not* a focus of study. However, what makes interneurons exciting to researchers and the reason they may play a primary role in understanding cortical function is that as a group interneurons are, simply, *diverse*. Whereas pyramidal neurons, despite their large raw numbers, are relatively stereotyped showing only marginal diversity in terms of morphology, genetics, and single neuron dynamics and response profile (such that they are rarely sub-classified in a manner that is not location specific) [Peters & Sethares 1991; DeFelipe & Farinas 1991] interneurons show remarkable diversity along each dimension (morphology, genetics, and single neuron dynamics) and are readily broken into distinct classes (*morphology*-[Cajal 1911; White 1989; Kawaguchi & Kubota 1997; Gupta, *et al.* 2000], *genetics*-[Kawaguchi & Kubota 1997; Xu, *et al.* 2004; Butt, *et al.* 2004; Dasen, *et al.* 2005], *response profile*- White 1989; Gupta, *et al.* 2000; McCormick & Bal 1997; Cauli, *et al.* 1997]). Conservative estimates put the number of IN types at ~20, with estimates ranging from 2 to a near-infinite number [Cauli, *et al.* 1997; Lorente de No 1992; Kawaguchi & Kubota 1996; Parra, *et al.* 1998; Markram, *et al.* 2004]. However, it is not merely the diversity of features alone that makes interneurons promising—on the theoretical side it is the fact that that diversity clusters into group with related properties including their input-output relationships and inter-type connection statistics and on the practical side it is the fact that a large percentage of that diversity can be clustered along genetically definable classes. This means that interneurons may provide a structured form of neural diversity

that naturally filters input statistics and that we can experimentally investigate that structure practically using modern genetic methods.

I.3 Genetically Identified Classes of Cortical Interneurons

While, obviously, genetic expression allows for almost limitless classification of neurons the most useful genetics classifications are those that define large, mutually exclusive groups with clear and distinguishable group characteristics with simple markers. Among interneurons there are currently three primary markers meeting these criteria: expression of the calcium binding protein parvalbumin (PV), the neuropeptides somatostatin (SOM), and the ionotropic serotonin receptor 5HT3a. Expression of each marker is exclusive (as detected by immunofluorescence), captures between 20-40% of interneurons, and encompasses distinct classes of interneurons. Each marker also carries unique and important biological functions itself, though how those functions impact the function of the neural classes they define is not currently known. Combined, the three markers appear to account for 100% of cortical interneurons in the mammalian cortex (though most extensive studies of interneuron genetics have been confined to rodent models). Within each class there are at least two major non-genetically defined sub-classes, with further, less well characterized subdivisions thereof. Notably, none of the current major subdivisions, defined independently from any genetic markers appear to contain members from more than one of the aforementioned classes.

PV and SOM interneurons have been studied the longest of the three classes [Kawaguchi, *et al.* 1987; DeFelipe, *et al.* 1989; Hendry, *et al.* 1989; DeFelipe 1993; Cauli, *et al.* 1997; Gonchar & Burkhalter 1997; Kawaguchi & Kubota 1997; Markram, *et al.* 2004; Somogyi & Klausberger 2005; Ascoli, *et al.* 2008] with 5HT3a interneurons as a primary class being a relatively recent discovery [Morales & Bloom 1997; Ferezou, *et al.* 2002; Puig, *et al.* 2004; Lee, *et al.* 2010] with less characterization [Lee, *et al.* 2010]. PV neurons make up between 25-50% of interneurons depending on layer and SOM neurons make up between 20-40% (layer II/III being split 35%/25%, respectively). Morphologically the two major classes of PV interneurons are basket cells and chandelier cells, which

target the soma and axon initial segment of innervated cells, respectively. Defined by spiking activity both groups and PV cells in general are also fast spiking (FS) cells, which is discussed further below. The two major classes of SOM interneurons are Martinotti and X94 cells, both of which target apical and basal dendrites of innervated cells. The two populations both receive strong cholinergic inputs and differ primarily in cortical layer distribution and targeting. Martinotti cells may also be from two primary sub divisions (distinguishable based on calretinin (CR) expression) with different cortical layer distributions and inputs. Though it is too early to say whether this subdivision is a relatively unique property of Martinotti cells or one of many finer IN subdivisions for which a clean genetic marker has simply been found.

The most striking difference between PV and SOM interneurons, however, from a cortical dynamics perspective is the presence of facilitating (excitatory) synapse in SOM interneurons (both Martinotti and X94 cells) and their general absence in PV interneurons (both basket and chandelier cells - though a small subgroup of PV interneurons, multipolar bursting (MB) cells does contain facilitating excitatory synapses). The possession or lack of this property is the primary determinant of a major difference in response profiles among PV and SOM neurons: adaptation or facilitation of response to excitatory inputs.

I.4 Adapting and Facilitating Responses in Neurons

Two key functional classes of neurons have been consistently found *in vitro*, where high-resolution analysis of neural activity and fine stimulus control enables quantitative descriptions of input-output relationships. "*Adapting*"-type neurons show large and reliable excitatory post-synaptic potentials (EPSPs) when presented with single, isolated pre-synaptic spikes. However, as the rate of pre-synaptic spiking increases, the size and reliability of EPSPs decrease [Deuchars & Thomson 1995; Reyes, *et al.* 1997; Galarreta & Hestrin 1998; Gibson, *et al.* 1999; Beierlein, *et al.* 2000; Koester & Johnston 2005; Goldberg & Yuste 2005; Tan, *et al.* 2008]. This finding contrasts with "*facilitating*"-type neurons that show initially small and low-reliability EPSPs (high

failure rate and high variability) in response to single pre-synaptic spikes. As the rate of pre-synaptic spikes increases their EPSPs become larger and more reliable [Tan, *et al.* 2008; Porter, *et al.* 2001; Beierlein, *et al.* 2003; Wang, *et al.* 2004; Kapfer, *et al.* 2007; Silberberg & Markram 2007]. A number of other functional features are associated with adapting- and sensitizing-type neurons, including EPSP rise times (slower in sensitizing neurons) [Tan, *et al.* 2008; Porter, *et al.* 2001; Beierlein, *et al.* 2003; Kapfer, *et al.* 2007; Silberberg & Markram 2007; Sun, *et al.* 2006; Cruikshank, *et al.* 2007] and EPSP co-efficient of variation (initially higher in sensitizing neurons) [Galarreta & Hestrin 1998; Tan, *et al.* 2008; Porter, *et al.* 2001; Beierlein, *et al.* 2003; Kapfer, *et al.* 2007; Silberberg & Markram 2007; Sun, *et al.* 2006; Cruikshank, *et al.* 2007].

Generally, adapting-type neurons are maximally active at input frequencies ≤ 10Hz [Tan, *et al.* 2008; Porter, *et al.* 2001; Beierlein, *et al.* 2003; Kapfer, *et al.* 2007; Silberberg & Markram 2007; Markram, *et al.* 1998] and sensitizing-type neurons at >10Hz [Tan, *et al.* 2008; Beierlein, *et al.* 2003; Silberberg & Markram 2007]. The frequency at which they bifurcate in their frequency-dependent dynamics maps to an important range of active sensing behaviors in mice and rats: *whisking*, discussed further below [Carvell & Simons 1996; O'Connor, *et al.* 2002; Nicolelis, *et al.* 1995; Berg & Kleinfeld 2003; Fee, *et al.* 1997; Sachdev, *et al.* 2001]. Because of this difference in preferred input frequency and their distinct dynamics, it has been theorized that adapting-type and sensitizing-type neurons engage in different sensory computational tasks *in vivo* [Moore, *et al.* 1999; Moore 2004].

I.5 Fast-Spiking IN and Pyramidal Cells Adapt, Low-Threshold Spiking IN Facilitate

Adapting and sensitizing types also predict neurons' spike shape and response to current injection [Nunez, *et al.* 1993; Simons 1978; McCormick, *et al.* 1985; Swadlow 1989; Wilson, *et al.* 1994]. Two classes of neuron are generally identified in the cortex by these other metrics: Fast Spiking cells (FS) and Regular Spiking cells (RS). The FS are characterized by narrow action potentials, deep fast after-hyperpolarizations (AHPs),

and lack of an adapting response during current injection [Nunez, *et al.* 1993; Wilson, *et al.* 1994]. RS are characterized by broader action potentials, long but shallow AHPs, and adaptation to current injection [Nunez, *et al.* 1993; Wilson, *et al.* 1994]. The FS and RS make up ~10-20% and ~80-90% of cortical neurons, respectively [Nunez, *et al.* 1993; Wilson, *et al.* 1994; Steriade, *et al.* 2001]. A key RS sub-population are Low-Threshold Spiking cells (LTS). These cells are similar in action potential behavior to RS, but show a characteristic "rebound" depolarization following hyperpolarizing current injection, sometimes leading to spike bursts [Kawaguchi & Kubota 1997; Kawaguchi 1993; Halabisky, *et al.* 2006]. The FS are inhibitory interneurons (IN) [Kawaguchi & Kubota 1997; McCormick, *et al.* 1985], and RS are primarily excitatory neurons, specifically pyramidal cells (PYR) [Simons & Carvell 1989; Hwa & Avoli 1992; Schwindt & Crill 1999; Chagnac-Amitai, *et al.* 1990]. Unlike most RS, LTS are usually IN [Beierlein, *et al.* 2003; Silberberg & Markram 2007; Ma, *et al.* 2006]. These categories map to the functional types mentioned above. *In vitro* studies indicate that FS and RS adapt and LTS sensitize.

I.6 SOM and PV Markers Identify LTS IN and FS IN

The functional differences among different classes of neurons may stem from differences in inputs, intrinsic properties, or both. Studies in the neocortex show that parvalbumin (PV) expression maps to adapting IN [Tan, *et al.* 2008], and somatostatin (SOM) expression maps to sensitizing IN [Tan, *et al.* 2008; Kapfer, *et al.* 2007]. The PV and SOM proteins have important physiological roles, including calcium binding [Gerday & Teuwis 1972; Fillis 1996; Gillis, *et al.* 1984; Chard, *et al.* 1993] and release as modulatory neuropeptides [Inoue & Yoshi 1992; Srikant, *et al.* 1992; Bell, *et al.* 1995; Patel 1999], respectively.

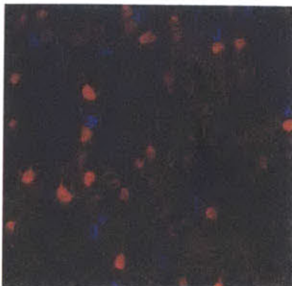

Figure I-1

Regardless of their role in functionality of cell types, PV and SOM expression can be readily detected by antibody staining or with gene coupled fluorescence expression in engineered mouse strains (please see below), and these markers strongly predict a neuron's functional properties. **Figure I-1** shows an example from

my laboratory of a coronal section through barrel cortex with antibody labeling for SOM (red) and PV (blue).

I.7 Mouse Barrel Cortex as an Ideal Model System

A key benefit of barrel cortex as a model system is the one-to-one correspondence between individual peripheral sensors (vibrissae) and anatomically identified regions (barrels) in the somatosensory cortex [Woolsey & Van der Loos 1970]. This discrete relationship allows peripheral feed-forward signals to be anatomically correlated with specific cortical columns. Further, the cell types, circuit connections, and many dynamic properties of this cortex are well characterized, providing a unique opportunity to relate functional (e.g., neural coding in awake behaving animals) and circuit-level properties [Moore, *et al.* 1999; Fanselow & Nicolelis 1999; Agmon & Connors 1989, 1991, 1992].

The vibrissa sensory system is also an attractive model because it is a high-acuity tactile system in rodents. Rats can discriminate between spatial frequencies that vary by as little as 60μm (e.g., 1.00mm vs. 1.06mm gratings) with features having only 10μm in width and can detect 90μm shallow gratings [Carvell & Simons 1990; Guic-Robles, *et al.* 1992; Carvell & Simons 1995; Stuttgen, *et al.* 2006].

The use of mouse barrel cortex also provides access to new genetic tools in a high-performance cortex. Most important for the present studies, specific cell types can be identified by fluorescent markers. The two key mouse lines of interest for my work are the GIN (GFP-expressing Inhibitory Neurons) [Oliva, *et al.* 2000] and PV-Cre mouse strains. GIN mice selectively express enhanced green fluorescent protein (eGFP) in a subpopulation of SOM GABAergic IN in the hippocampus and neocortex. These eGFP expressing neurons are primarily located in layers II-Va and comprise ~1/3 of all SOM cells in layers II/III (where I will be collecting data; see below) [Oliva, *et al.* 2000].

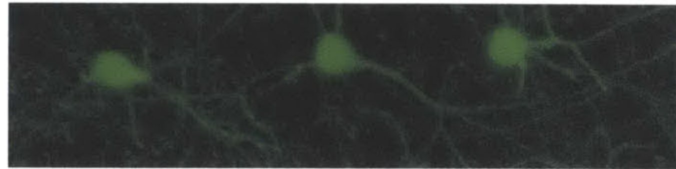

Figure I-2

Electrophysiological characterization of eGFP expressing neurons also indicates that they belong to the sensitizing class of SOM/LTS neurons previously mentioned [Halabisky, *et al.* 2006], are Martinotti-type cells [Ma, *et al.* 2006], and appear to be functionally equivalent to other SOM neurons in layers II/III [Cauli, *et al.* 1997; Kawaguchi & Kubota 1996; Halabisky, *et al.* 2006]. **Figure I-2** shows an example I collected of eGFP labeled neurons in a GIN mouse. The image is a 171μm wide 80μm deep Z-stack that has been collapsed to give an infinite focus image of three SOM neurons in layers II/III of the cortex (depth estimated at 150μm at center).

Preliminary and published studies in other labs reported that GIN neurons in layers II/III of both primary visual cortex (V1) and primary somatosensory cortex (SI) cannot be driven by visual or vibrissal (whisker) sensory stimulation, respectively [Zariwala, *et al.* 2009; Gentet, *et al.* 2012]. Though, whereas Zariwala, *et al.* simply found GIN neurons to be robustly silent Gentet, *et al.* found GIN neurons to be *highly* active when animals were *not* exposed to stimuli and strongly suppressed during stimulation. Inconsistent with those results, we have found that GIN neurons in layers II/III of SI show robust and consistent responses to electrically induced whisking. The reasons for this different finding are unclear, and could pertain to electrical whisking being a more natural stimulus than visual gratings, differences in visual and somatosensory cortex dynamics, or myriad subtle technical differences in technique. Both findings run contradictory to results predicted by *in vitro* experimental findings and my own findings (presented later). Gentet, *et al.*'s work [2010; 2012; 2013] is the most developed and directly relevant to my own. It examines the firing PYR, FS (PV), non-fast spiking (putatively 5-HT), and SOM neurons IN in awake mice during periods of free whisking in air, whisking against a contact, and during quiet waking. Gentet, *et al.* found that PYR, NFS and FS neurons showed low activity levels during "quiet" (low stimulation) periods and high activity during free whisking (high stimulation periods) and showed sensory responses to passively applied and active whisk-driven contact sensory events [XXX]. GIN neurons showed dynamics opposite those predicted by *in vitro* studies: They displayed high firing rates during quite periods and strong suppression during free whisking with the surprising finding of hyperpolarization with external whisker stimulation.

In anesthetized/narcotized mouse primary visual cortex Kerlin, *et al.* 2010 focused on the stimulus selectivity properties of IN during stimulation. While there is current disagreement over the degree of selectivity exhibited by FS, both groups agree (contrary to Gentet, *et al.*) that this cell population is readily driven by sensory input. The Kerlin, *et al.* 2010 findings also show, in agreement with [Ma, *et al.* 2010], that SOM IN in layers II/III are sensory responsive in V1. In awake mouse V1, Adesnik, *et al.* [2012] have also found robust SOM responses to sensory input.

The use of volitional whisking as a source of sensory stimulation, while ethological, creates ambiguity regarding the sensory versus volitional or efference-copy inputs to layer II/III IN in SI. As volitional free whisking is known to be controlled or impacted by numerous cortical and non-cortical processes that present top-down, lateral, or other inputs to SI (e.g. efference copies from motor cortex [Christensen, *et al.* 2007; Witham, *et al.* 2010] or arousal related sensory modulation [Trageser, *et al.* 2006; Urbain & Deschenes 2007]) the loosely understood timing and impact of many factors

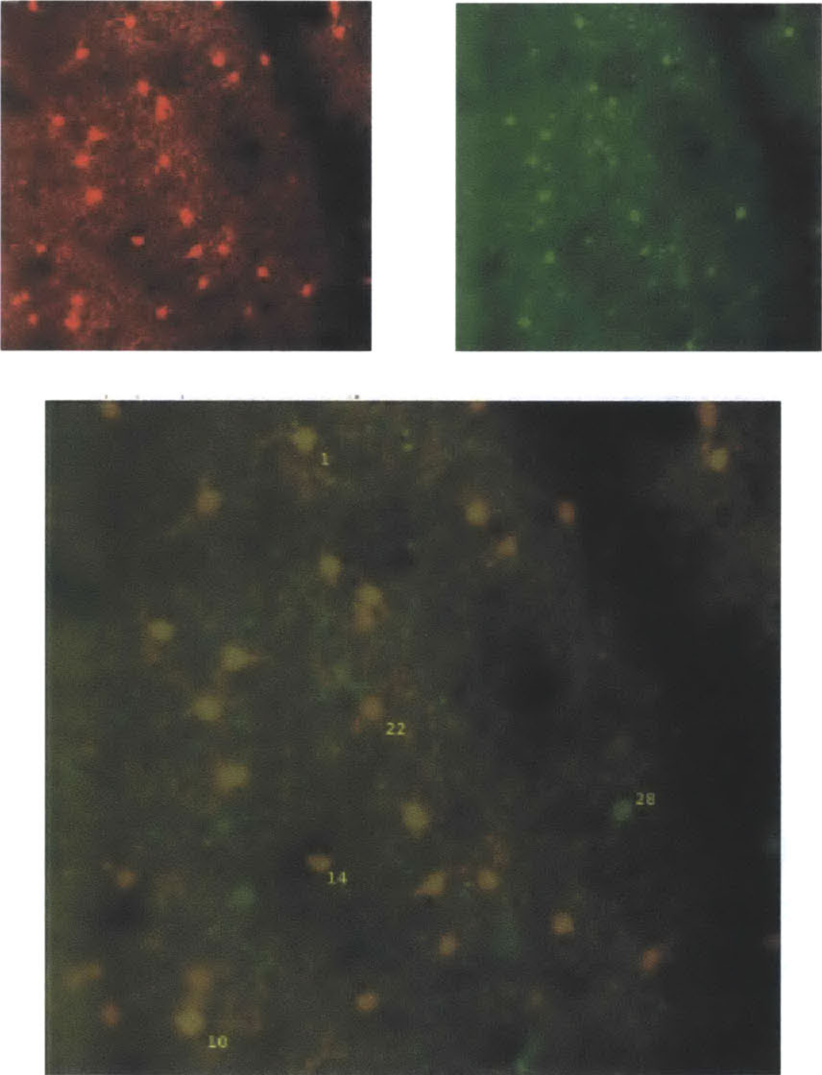

Figure I-3

which can precede or co-occur with whisking related, bottom-up thalamocortical sensory stimulation serious complicate any interpretation of IN dynamics in the context of sensory stimulation. We have done our best to address both of these issues by: Breeding a mouse line that expresses distinct markers for both PV and SOM without any apparent functional abnormalities allowing us to study the responses all of our target populations simultaneously. And by using electrical whisking in a lightly anesthetized mouse to minimize non-sensory related variations in inputs to our IN populations to allow for a cleaner theoretical dissection of our results.

The PV-Cre line has been bred by my lab with a fluorescent reporter line to allow selective imaging of PV/FS neurons. For my study, Pv-Cre mice will be crossed with an eGFP expressing reporter line (e.g., R26R-eGFP). The PV-Cre transgenic we use has ≥ 97% specificity to PV IN in neocortex [Kuhlman & Huang 2008], findings confirmed in recent studies in my lab [Cardin, *et al.* 2009]. **Figure I-3** shows PV antibody staining (bottom panel), PV-Cre intrinsic fluorescence (middle), and their overlap (top) in adult mouse neocortex.

I.8 Whisking and Quiescence as Two Discrete States

Animals use different sensory behaviors to perform different perceptual tasks. In primate vision, animals make repeated saccades to enhance object recognition and smooth pursuit motions to track objects [Rashbass 1961]. These behaviors presumably optimize acquisition of sensory information and are accompanied by changes in neural activity that reflects different processing states [Moore, *et al.* 1999; Nicolelis & Fanselow 2002]. In the rodent vibrissa system, the most pronounced example of a change in sensory context is "whisking" [Vincent 1912; Welker 1964; Wineski 1985; Harvey, *et al.* 2001]. In rats, whisking typically consists of sweeping the vibrissae back and forth along the anterior-posterior axis in an elliptical motion at ~5-15Hz [Carvell & Simons 1996; O'Connor, *et al.* 2002; Nicolelis, *et al.* 1995; Nicolelis & Fanselow 2002; Berg & Kleinfeld 2003; Fee, *et al.* 1997; Carvell & Simons 1990; Carvell & Simons 1995; Vincent 1912; Wineski 1985; Guic-Robles, *et al.* 1989; Milani, *et al.* 1989; Sachdev, *et al.* 2002; Brecht, *et*

al. 2004; Hill, *et al.* 2008]. The motions are stereotyped, typically symmetrical, and presumably controlled by a central pattern generator outside of the cortex, most likely in the brain stem [Gao, *et al.* 2001; Nguyen & Kleinfeld 2005; Hattox & Keller 2003; Hattox 2003]. Whisking epochs are typically isofrequent within a bout, which lasts from 1-15 seconds [Berg & Kleinfeld 2003]. The transitions from whisking to non-whisking are commonly reported as being sharp and readily detected, a finding I have confirmed in my mouse model system (please see the Behavior section of Research Design & Methods).

Whisking is selectively engaged based on task. Whisking, for example, occurs during tasks involving texture discrimination [Carvell & Simons 1995; Harvey, *et al.* 2001] and during exploratory behaviors [Hutson & Masterton 1986; Knutsen, *et al.* 2005]. Whisking does not appear to be engaged or necessary during other tasks, including deflection detection [Stuttgen, *et al.* 2006] and bilateral distance discrimination of the size of a gap opening [Krupa, *et al.* 2001; Shuler, *et al.* 2002].

Most prior whisking studies were conducted in rats. Although some labs use mice in headposted preparations, there are currently no papers examining whisking in freely behaving mice, and the detailed kinematics of headposted whisking are not well studied. One difference, previously reported anecdotally [Woolsey & Van der Loos 1970; Ferezou, *et al.* 2006] and replicated in free behavior studies in my laboratory [Ritt and Moore, unpublished observations], is that mice whisk at higher frequencies, from 12-30Hz. While not the focus of my study, I will obtain quantitative data on this topic that should contribute to this emerging literature.

There are likely many ways that whisking enhances sensory processing in rodents. Whisking is thought to facilitate fine-feature detection and discrimination by increasing the rate of tactile sampling of an object and by generating contrast through motion of the sensory vibrissae [Ritt, *et al.* 2008; Carvell & Simons 1990; Andermann, *et al.* 2004; Moore & Andermann 2005; Hipp, *et al.* 2006]. A second idea is that the sensory feedback generated at the whisking frequency adapts barrel cortex neurons. This different state of cortical processing may benefit perceptual tasks requiring the more localized sensory representations observed in adapted neurons [Moore, *et al.* 1999; Moore 2004].

Differential recruitment of IN by whisking—which I will test in this proposal—is one mechanism for the selective expression of sharpened receptive fields at specific rates of afferent stimulation.

1.9 Neural Coding of Whisking: Some Neurons in Barrel Cortex Are Driven by Whisking

Neural recordings during whisking show whisking-dependent activity in cortical, sub-cortical, and peripheral neural stations. Under anesthesia and using electrically induced whisking, Ahissar, *et al.* have demonstrated sub-populations of whisking responsive cells in the first-order neurons of the trigeminal ganglion [Szwed, *et al.* 2003] and separate pathways are hypothesized to exist that convey whisking and non-whisking related information in the thalamus [Yu, *et al.* 2006]. In the trigeminal ganglion, whisking responsive cells fire at specific phases in a whisk cycle, providing an accurate measure of whisker position [Szwed, *et al.* 2003]. In paralemniscal and lemniscal ascending pathways in the thalamus, cells selectively respond to whisking motion and contact during whisking [Yu, *et al.* 2006]. In the cortex, whisking-selective activity has been demonstrated in the form of phase locking of cortical action potentials to the whisk cycle [Fee, *et al.* 1997; Crochet & Petersen 2006] and a strong positive correlation observed between cortical low-frequency potentials and whisking amplitude [Fee, *et al.* 1997; Crochet & Petersen 2006; Ahrens & Kleinfeld 2004; Ganguly & Kleinfeld 2004]. Chemical blockade of the facial motor nerve eliminates the fast-oscillatory component of whisking-related activity in barrel cortex, indicating that phase-locking is dependent on sensory transduction rather than lateral ("corollary") discharge from the motor cortex or a related area [Fee, *et al.* 1997].

While neural whisk-responsiveness is observed in single neurons, these responses are not uniform. In the trigeminal ganglion, some cells show no whisk responsiveness, only responding to passive contact signals [Szwed, *et al.* 2006]. Similar response profiles are seen in the extralemniscal ascending pathway of the thalamus, which also conveys contact related signals during non-whisking periods [Yu, *et al.* 2006]. The greatest

variability appears to arise in the cortex. In Fee, *et al.*, the percentage of cells that show phase-locking to the whisk cycle is only 57%, and even then with highly variable degrees of modulation and at different phases of the whisk cycles in different neurons [Fee, *et al.* 1997]. Only 43% of single units firing showed correlation with whisk amplitude. The diversity of whisk-response relationships in SI may be, in part, a function of underlying neural diversity. Distinct cell types, such as different IN types, may be one source of the distinct responses observed during whisking.

1.10 Headposted Whisking as a State that Can be Controlled

Many techniques are difficult to perform on awake, freely moving animals. One means of applying techniques that require stability to awake animals is through the use of headposted preparations. Headposting requires surgical attachment of a post to the skull by which an animal's head can be stabilized through attachment to an external frame. 2-photon imaging has been successfully used in headposted animals, and the technique has been successfully used to study barrel cortex during whisking and quiescent sensory states in rats [Sachdev, *et al.* 2001; Brecht, *et al.* 2004; Gao, *et al.* 2001; Bermejo & Zeigler 2000] and mice [Dombeck, *et al.* 2007].

I.11 In Summary

Interneurons represent a large and complex class of unknowns that may help elucidate general brain function and in particular may serve as a source of cortical dynamic regulation. Two of the largest classes of IN, parvalbumin neurons and somatostatin neurons, consistently present opposite gross dynamic profiles on the single neuron level *in vitro*. At a minimum their tendency to adapt or facilitate in response to inputs and the mutually antagonistic connections of the PV and SOM IN networks suggests that the two IN classes should be differentially active during high-activity periods in the cortex, such as during sensory active sensory behaviors like whisking in the rodent. If so, PV and SOM IN appear to be perfectly suited to maintain different

dynamic environments in the same area of cortex based purely on sensory input—a remarkably elegant tool for implementing task-dependent computational flexibility.

However, contrary to the expectations drawn from single neuron and small-network *in vitro* recordings the few studies investigating IN properties *in vivo* have found results both inconsistent with those expectations and with each other (with vastly different results even coming from the same lab). Though initially discouraging one possibility explaining the diverse *in vivo* results is ambiguity stemming from cortically top-down, bottom-up, and lateral inputs to IN. This is especially true in the studies in SI where *spontaneous* (voluntary) whisking was used as a sensory source; meaning that bottom-up inputs to SI IN were almost certainly preceded by top-down and lateral inputs from M1 and other cortical and non-cortical areas responsible for induction of whisking behavior. To address that problem we set-up an anesthetized *in vivo* prep that utilized direct and external electrical induction of muscle movement to produce "artificial whisking". That presented inputs to SI that are naturalistic and closely simulate the natural behavior of "free whisking" while avoiding introduction of ambiguous top-down or lateral signals (e.g. motor cortex or arousal associated signals). Additionally, the use of animals with differentially fluorescent tagged PV and SOM IN allowed us to directly compare, within a trial, time courses of IN response with much greater statistical power than the use of separate animals for separate IN classes would have.

Chapter 1

Emulated Whisking Drives SOM Interneurons in Anesthetized Mouse SI Neocortex

1.1 Author Contributions

This work is derived from a paper written by myself (Ethan Skowronski-Lutz[1]) and Christopher I. Moore[1, 2].

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1.2 Abstract

The brain contains a diverse array of interneurons that exhibit different morphologies, chemical identities, electrophysiological profiles, and connectivity. Recent studies in the vibrissal primary somatosensory neocortex (SI) have observed that somatostatin-positive interneurons (SOM) show hyperpolarizing responses to passive sensory input and decreased firing rates during whisking. In contrast, in the mouse primary visual neocortex (V1), robust sensory activation of this same cell class has been observed in anesthetized and awake preparations. These distinctions suggest either that SOM are uniquely isolated from effective excitatory sensory input in SI, or that the conditions under which their properties have been measured are crucial to this unique observation of suppressed activity with novel sensory drive. Specifically, in the awake *in vivo* condition, SOM show high background firing rates, and this context of activity may be essential to prior findings. To directly test whether SOM can respond to sensory drive, and to compare the responses of this cell class to other well-described types, we investigated the *in vivo* dynamics of functionally and genetically separate classes of neocortical interneurons with 2-photon imaging of calcium dynamics in mouse barrel neocortex. The three classes of neurons we tested were identified as SOM (marked by fluorescence in the GIN mouse), parvalbumin (fast-spiking PV neurons), and 'other' (putative pyramidal neurons, PYR). These groups showed distinct responses and neural dynamics during emulated active sensation (electrical whisking) and vibrissa stillness. The PV and PYR classes showed a robust onset response to vibrissal stimulation that typically adapted. GIN/SOM neurons, in direct contrast to recent reports in barrel cortex, also showed a robust onset response, and this response further enhanced with sustained stimulation.

Between-neuron correlations were also distinct, as PV and PYR neurons showed moderate correlations within class during baseline and at the onset of vibrissal stimulation, while GIN did not. In contrast to the sensory-evoked increases in calcium levels in GIN neurons after stimulus onset, no significant correlations were observed within this type immediately post-stimulus, continuing the pre-stimulus status. However, with sustained input, this class showed increasing levels of correlation throughout the 4 seconds of drive. The overall strength of within-class correlations was significantly greater for the peak of GIN cell activity than for any epoch observed in either of the other classes. These data support the view that PV and GIN interneurons have substantially different sensory-driven neural dynamics, suggesting they impact information processing in distinct ways during time-evolving sensory perception. They also show that SOM interneurons can demonstrate robust and rapid sensory-driven responses, indicating the importance of state for prior observations of the non-recruitment of this cell type.

1.3 Introduction

A fundamental question in systems neuroscience is what factors drive a single neocortical circuit (e.g. in primary somatosensory neocortex, SI) to demonstrate distinct processing states. Prior theoretical work has proposed that SI barrel neocortex may be optimal for the detection of sensory stimuli when not adapted to sensory inputs and, in contrast, for discrimination between stimuli after the onset of sensory drive [Moore, *et al.*, 1999; Moore, 2004; Wang, *et al.*, 2010]. Interneuron diversity in their responsiveness to sustained sensory input may provide one mechanism for shifting dynamics within a neocortical network among such optimal processing modes [Moore, *et al.*, 2010]. Interneurons strongly impact the rate and the timing [Issacson & Scanziani 2011] of evoked neural activity, and are believed to be critical to the generation of behavioral states associated brain rhythms [e.g. Buzsaki, 1983; Traub and Whittington, 1992; Hausenstaab, *et al.*, 2005; Cardin, *et al.*, 2009], suggesting they are key in the control of such local dynamics in the brain.

1.4 Different *In Vitro* Dynamics Predict the Emergence of Different Sensory Responses Across Interneuron Types

Interneurons expressing the neuropeptide somatostatin (SOM) and those expressing the calcium binding protein Parvalbumin (PV) are almost entirely non-overlapping 'types' in the neocortex [Rudy, *et al.* 2011], and show complementary dynamic profiles in studies of paired neuron recordings *in vitro*. With sustained presynaptic pyramidal neuron firing, SOM neurons facilitate [Tan, *et al.* 2008; Kapfer, *et al.* 2007] while PV neurons adapt [Tan, *et al.* 2008]. These two classes also form networks that are gap-junction connected within-type, and show GABA mediated suppression within and between types [Gibson, *et al.* 1999; Beierlein, *et al.* 2000]. These properties indicate the two classes form networks that can be mutually antagonistic, defined in part by dynamics in rate of activity and in expression of correlations within-type. Such antagonism has been shown using computational modeling in our laboratory to be a viable explanation for observed oscillatory dynamics *in vivo* [Vierling-Classen, *et al.*, 2010].

The frequency of presynaptic firing at which SOM and PV neurons' response rates show significant facilitation or adaptation is approximately ≥ 10Hz [Tan, *et al.* 2008; Beierlein, *et al.* 2003; Kapfer, *et al.* 2007; Silberberg & Markram, 2007; Markram, *et al.* 1998]. This rate is near the mean whisking frequency of rats during exploratory whisking [Vincent 1912; Carvell & Simons 1990, 1995, 1996; O'Connor, *et al.* 2002; Berg & Kleinfeld 2003; Sachdev, *et al.* 2002; Hill, *et al.* 2008] and within the whisking frequency of mice, which can be as high as 15-20 Hz [Woolsey, *et al.*, 1980; Voigts, *et al.*, 2008]. These *in vitro* studies suggest that sensory drive in the behaviorally-relevant whisking range should differentially engage these two interneuron types.

In anesthetized/narcotized mouse primary visual cortex, Runyan, *et al.* 2010, 2013 and Kerlin, *et al.* 2010 measured the stimulus selectivity properties of IN during stimulation. While there is current disagreement over the degree of selectivity exhibited by FS, both groups agreed that this cell population is readily driven by sensory input. The

Kerlin, *et al.* 2010 findings also showed, in agreement with [Ma, *et al.* 2010], that SOM IN in layers II/III are sensory-responsive in V1. In awake mouse V1, Adesnik, *et al.* [2012] have also found robust SOM responses to sensory input. Further, these authors observed that the unique spatial summation properties of SOM IN appear to be the basis for center surround inhibition in V1 PYR. This finding generally agrees with the view that engagement of SOM reflects a distinct mode of enhanced discriminative process in SI neocortex [Moore, *et al.*, 2010].

1.5 In Contrast to V1, Initial Reports Indicate *Suppression* of SOM with Sensory Input in SI

In contrast to the V1 observations in anesthetized and awake mice showing consistent SOM activation with sensory drive, findings in SI of awake mice have uniformly reported suppression of this cell type with sensory input or sensorimotor activity. Gentet, *et al.* [2010] found that PYR, putative 5-HT3a and FS showed low activity levels during "quiet" (low stimulation) periods and high activity during free whisking (high stimulation periods), and showed sensory responses in all these types to passively applied and active whisk-driven contact sensory events [Gentet, *et al.* 2010; 2012]. In a subsequent study, these authors found that SOM (GIN) interneurons displayed high firing rates during quite periods and strong suppression during free whisking, with the surprising finding of hyperpolarization with external vibrissal stimulation [2012]. More recently, Lee, *et al.* [2013] have confirmed these results, showing increased firing rates in VIP (5-HT3a) positive interneurons and decreased firing rates in SOM in association with bouts of free whisking in air. These authors further showed that inactivation of the vibrissal M1 representation revealed variation in the response of these cell classes, with significant increases and decreases in both types during whisking (as opposed to entirely the uniform behavior that was observed within type with intact vM1). **These findings in SOM in SI pose a specific and important question. Are SOM in SI unable to be driven to robust spiking by sensory input under all conditions, or are these recent findings dependent on the measurement context in which they were made, the awake, head-posted**

mouse exhibiting free whisking?

In favor of the 'state' dependence of this SOM suppression, these cells exhibit high firing rates in the awake state not observed under anesthesia [Deister, Skowronski-Lutz, and Moore, unpublished observation], positioning SOM to reveal inhibition that might not have been recognized otherwise. However, in the Adesnik, *et al.* [2012] study in V1, they also observed high baseline rates in SOM that did not predict the revelation of sensory-driven suppression, indicating the 'state' of ongoing activity patterns does not generalize across brain areas as a requirement for suppression. In favor of the contrasting view that SOM could be uniquely synaptically 'isolated' from effective excitatory sensory drive in SI, these cells do not receive feedforward excitatory input from layer IV glutamatergic neurons in this neocortical area [Adesnik, *et* al. 2012].

1.6 Emulated Whisking as a Model Stimulus for Testing SI Dynamics

The use of volitional whisking in awake mice as a source of sensory stimulation, the primary context that has led to the claim that SOM are uniquely suppressed, is problematic when trying to understand the response of these cells. Volitional whisking in the head-posted mouse is somewhat ethological, though whisking in real exploration is almost always accompanied by head motion and by the goal of sensory exploration [Ritt, *et al.*, 2008]. Further, as directly shown by Lee, *et al.* [2013], substantial descending 'efference copy' from vM1 is present in SI during whisking, which putatively suppresses SOM activity to sensory drive. A preparation that isolates the 'reafferent' component of whisking (the sensory input generated by the act of moving) from other potential contaminants is the 'electrical whisking' preparation. This preparation, introduced by Zucker and Welker as a means to study active sensing in anesthetized rodents [Zucker and Welker 1969; Brown & Waite 1974] and reintroduced to the field more recently by Ahissar, *et al.* [Szwed, *et al.* 2003], also known as "artificial whisking", uses direct electrical stimulation of the facial motor nerve (cranial nerve VII) to elicit high-frequency whisker motion mimicking the statistics of vibrissa motion during active sensation without requiring cortical and sub

cortical mechanisms that would otherwise drive such an event [Fee, *et al.* 1997; Berg & Kleinfeld 2002; Ahrens, *et al.* 2004]. The motor nerve is cut to prevent the whisker driving electrical impulses being carried back to the central nervous system or stimulating any other cranial nerves (as many join paths closer to their point of emergence from the skull). This kind of stimulation has been shown to drive robust sensory responses in all layers of SI in anesthetized rats [Szwed et al., 2003].

I.7 Use of GIN Mice

To systematically test the potential differential responses of FS and SOM to sensory drive, and their different spontaneous (i.e., correlational) dynamics, we bred a mouse line that expressed distinct fluorescent markers for PV and SOM. Specifically, as in the Gentet, *et al.* [2012] paper, we employed the 'GIN' mouse line to selectively identify a subset of SOM interneurons. In this mouse line, only SOM neurons are labeled, and the identified subset are largely electrophysiologically indistinguishable from unlabeled populations [Xu, *et al.* 2004; Kawaguchi & Kubota 1996; but see Halabisky, *et al.* 2006]. Most critically for the current logic of experimentation, GIN show facilitating dynamics *in vitro* [Tan, *et al.* 2008; Kapfer, *et al.* 2007; Halabisky, *et al.* 2006; Hwa & Avoli 1992]. GIN neurons, and SOM neurons in general, are not strictly homogeneous; different authors have proposed meaningful subgroups based on morphological (multi-, bi-, or uni- polarity), electrophysiological (principally decay time), or biochemical (principally presence of Calretinin) properties of individual cells. However, even where cases can be made for functionally relevant clusters within this type (e.g. Calretinin predicts layer based connectivity): (1) no proposed SOM sub-division fails to show the general SOM characteristics of facilitating excitatory synaptic dynamics *in vitro*; (2) there is no evidence that the within-class diversity among SOM neurons even approaches the between class diversity among SOM and PV neurons or SOM and PYR neurons—making the class *relatively* homogenous for the generalizations drawn in this study; (3) GIN neurons do not appear to show any functionally relevant differences from SOM neurons besides expression of eGFP and density within a layer [Oliva, *et al.* 2000; Ma, *et al.* 2006; Xu, *et al.* 2006; Halabisky, *et al.* 2006; McGarry, *et al.* 2010].

We employed 2-photon imaging of calcium signals to track activity over the time scale of sustained stimulation across several seconds using bulk-loaded calcium dyes. These studies were conducted in the lightly anesthetized mouse.

1.8 Summary of Findings

These studies generated three key findings. First, **we observed robust sensory responses at the onset of sensory stimulation in SOM.** This finding directly demonstrates that the prior observations of SOM suppression are highly state dependent. Second, we observed distinctly different dynamics between SOM and PV that evolved over the time course of seconds. Sensory driven responses adapted with sustained stimulation in FS/PV and in putative pyramidal neurons, while SOM showed relative facilitation or sustainment of response amplitude. Third, the three classes of neurons showed distinctly different *internal correlation* dynamics. Pyramidal cells showed an almost immediate decorrelation (with themselves) upon onset of stimulation followed by rapid decorrelation of PV (again, with themselves) after about 1.2 seconds. In contrast, SOM showed a moderate within-class increase in correlation at ~0.5 seconds, about the time that PYR within-class correlation plummets, followed by a much larger correlation at about 1.2 seconds that is sustained for the stimulation period. The fact that the correlational structure of these three classes of neuron are almost exclusionary in their time courses seems reinforces the view that these are antagonistic networks with regards to their dynamics. In sum, these data strongly support the general independence in the dynamics of these two cell classes relative to behaviorally relevant sensory stimulation *in vivo*, and the idea that each dominates network activity in relatively distinct phases of an ongoing sensory experience

1.9 Materials & Methods

Animal Strains

All techniques were performed in mouse strains developed to show florescence in genetically defined subsets of neurons. The first set of experiments solely employed GIN mice (strain FVB-TgN(Gad-GFP)45704Swn, Jackson Laboratories), which contain an eGFP labeled population of neurons within the class of SOM interneurons. The eGFP label was sufficient to determine that the labeled neuron was SOM. It also, statistically, allowed us to make the inference that any other neuron was highly likely (>80%) to by PYR. The second set of experiments employed a new line of triple crossed mice that I bred for these experiments; the mice were a cross of GIN mice with PV-Cre mice (strain C57/B16-TgN(PV-Cre) Jackson Laboratories) and floxed tdTomato mice. PV-Cre mice express Cre exclusively in PV expressing cells and so exclusively and almost entirely (>98%) label PV interneurons in cortex; crossed with floxed tdTomato mice the labeled cells express a fluorescent marker similar to, but distinguishable from, eGFP. The triple cross mice thus labeled almost all PV interneurons, roughly half of SOM interneurons, and allowed the strong statistical inference that ~90% of remaining neurons are PYR.

Surgical Technique

Mice were given an intramuscular injection of ketamine (80mg/kg) and xylazine (6mg/kg). The scalp hair was trimmed, lidocaine applied to the scalp cutaneously, the scalp resected, and the skull cleaned. A specially machined flat headpost with a circular opening covering the future craniotomy site was daubed with cyanoacrylate gel and affixed to the skull, the opening placed over barrel neocortex, ~3.5mm lateral to bregma and ~1mm posterior to lambda. Additional cyanoacrylate was then applied followed by methylmethacrylate to speed curing. The animal was secured for surgery and imaging by bolting the headpost flanges to two posts mounted atop a steel breadboard.

Craniotomy and Portal Preparation

A square craniotomy measuring ~0.80mm x ~0.80mm was made above barrel neocortex (1mm posterior to bregma and 3.5mm lateral) using a scalpel blade and fine forceps. This craniotomy size allowed full access to dye-loaded regions while minimizing motion caused by brain pulsation (mean motion was typically $< 2\mu m$). Following removal of the skull, the fine murine dura surrounding the cortex was removed by careful application of a hooked insulin syringe needle with the aid of magnification. Great care was taken to ensure that the needle never contacted cortex and instead that the dura mater was lightly hooked and lifted away from the cortex to rupture it. After the ruptured dura was visible and could be enlarged by hooking and pulling the dura without injuring the cortex below. Any injuries to cortex were immediately obvious both by feel and by profuse bleeding; injured animals were not used for data collection.

After this procedure, a Ca^{2+}–sensitive dye (Fluo-4 or Oregon Green Bapta) was injected [please see section <u>2-Photon Laser Scanning Microscopy</u>, below]. After injection, the silicon elastomer Kwik-Sil (Kwik-Sil adhesive, WPI) was mixed and lightly folded over the craniotomy site. Any bubbles that formed during this process were removed under magnification with the aid of an insulin syringe needle. Special care was taken when mixing the Kwik-Sil polymer to avoid air bubbles to begin with as removal is painstaking. Immediately after application of Kwik-Sil a 3mm diameter coverslip was placed on top of the Kwik-Sil and held down with light pressure applied via a rubber tipped rod. After approximately 15-30 min the Kwik-Sil had hardened and both held the coverslip in place and created a barrier protecting the cortex from exposure and drying.

Electrical Whisking

A dermal incision was made posterior to the vibrissa pad to expose the facial nerve. The anterior end of the buccal branch was cut, and the nerve held in a bipolar cuff electrode. The nerve was kept moist by saline application during surgery followed by application of Kwik-Sil (Kwik-Sil adhesive, WPI) for mechanical stability and to prevent drying during the experiment. Artificial whisking was generated by application of $40\mu s$

current pulses at 83 Hz through a stimulus isolation unit in 20Hz bursts. In a subset of headposted mice, I measured spontaneous whisking biometrics. I found that mice (N = 5) displayed intermittent, spontaneous whisking upon waking (within 10 minutes) and continued to intermittently whisk for the duration of the experiment (5+ hrs). For my sample, mean whisking duration in a bout was 3.22 seconds (standard deviation [SD] 3.60 seconds) and the mean inter-bout interval was 32.78 seconds (SD 41.04 seconds). **Figure 1-4** shows an example of the periodicity of whisking bouts and their relative durations from a GIN mouse. Dark bars indicate epochs of whisking; the lower panel is an expanded display of the gray overlay region in the panel above. Electrically induced whisking parameters (duration 6-8 seconds) and inter-whisk interval (60 seconds) were chosen to recapitulate these time frames, but with a bias toward longer durations to better explore evolution and plateauing of temporal dynamics and allow for cortical reset, between whisking bouts.

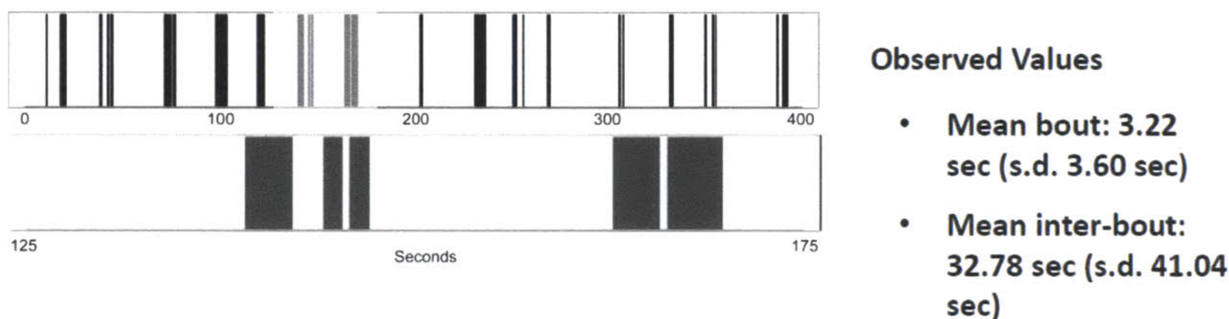

Figure 1-4

2-Photon Laser Scanning Microscopy

Experiments were conducted on a custom Prairie Ultima system (Ultima multiphoton microscopy system, Prairie Technologies) using Fluo-4 Ca^{2+}-sensitive dye (first experiment) and Oregon Green Bapta (OGB) Ca^{2+}-sensitive dye (second experiment). The peak two-photon absorption wavelength for both Fluo-4 and OGB (~820nm) is distinct from that of eGFP (~960nm), which allowed me to differentiate between intrinsic (eGFP) and functional (Fluo-4 or OGB) signals. Fluo-4 was dissolved in DMSO with 20% pluronic

acid and artificial cerebral spinal fluid. Dye was injected through a ~4μm tip diameter patch pipette ~200μm below the cortical surface.

After injection, the pipette was removed and the craniotomy sealed with 2% Kwik-Sil and a glass coverslip. I employed an Olympus BX-61W1 microscope (BX61W1 Multiphoton FV300 microscope, Olympus) coupled with a Mai Tai DeepSee (Spectra-Physics) mode-locked Ti:sapphire laser (>2.5W mode-locked laser, <100fs, 80MHz at 820nm) and use a 40x water immersion lens (LUMPLFLN 40XW, Olympus) to focus laser light. The imaging region consisted of a rectangle selected around areas showing both cells exhibiting both intrinsic and extrinsic sources of fluorescence gentically or injection derived fluorescence sources. All images were taken at a depth of 120-250 μm, corresponding to layers II/III in the mouse barrel neocortex, determined by zeroing depth to the imaging plane that focused the surface of the exposed brain and tracking movement of the focal point normal to that plane. Functional dye labeling in my experiments lasted 1-3 hours before a loss of signal due to dye bleaching or extrusion.

1.10 Results

We performed two sets of experiments, the first comparing GIN cells (N = 67 cells, 8 mice) to non-GIN neurons (N = 218 cells), and the second experiment in mice with distinctly identified GIN and PV cells, and non-identified, putatively pyramidal neurons (N = 58 GIN cells, 170 PV cells, and 323 PPYR cells, 6 mice). Our first experiment was designed to test if SOM cells showed increased activity during whisking-like stimulation *in vivo*, in contrast to the findings of Gentet [2012]. As in that study, we used the GIN mouse, in which ~1/3 of SOM neurons in layers II/III of neocortex express eGFP [Oliva, ea. 2000]. Cells were randomly labeled by bulk injection of the Ca^{2+}-sensitive dye Fluo-4, chosen for its high signal to noise ratio relative to other Ca^{2+} dyes. Non-GIN neurons labeled with Fluo-4 should predominantly be pyramidal (~>80%) [Rudy, *et al.* 2011]. The data were collected using single plane, whole image acquisition at 10-25 Hz. Fluo-4 labeled GIN neurons were distinguished from non-GIN neurons by means of different absorption spectra for Fluo-4 and eGFP (see ***Materials and Methods***).

Animals were anesthetized with ketamine and xylazine, head-posted, and imaged through a cranial window made directly before data collection. An artificial whisking preparation consisting of direct electrical stimulation of cranial nerve VII at 20 Hz induced vibrissa movements, and in turn the consequent 'reafferent' sensory drive. Artificial whisking bouts were randomized, lasted for 6 or 8 seconds, and occurred at intervals ranging from 20 to 75 seconds. Times were chosen based on observed values of spontaneous whisking in unanesthetized animals (see ***Materials and Methods***). **Figure 1-4** shows an example of the relative duration and inter-bout intervals of whisking in an untrained head-posted mouse.

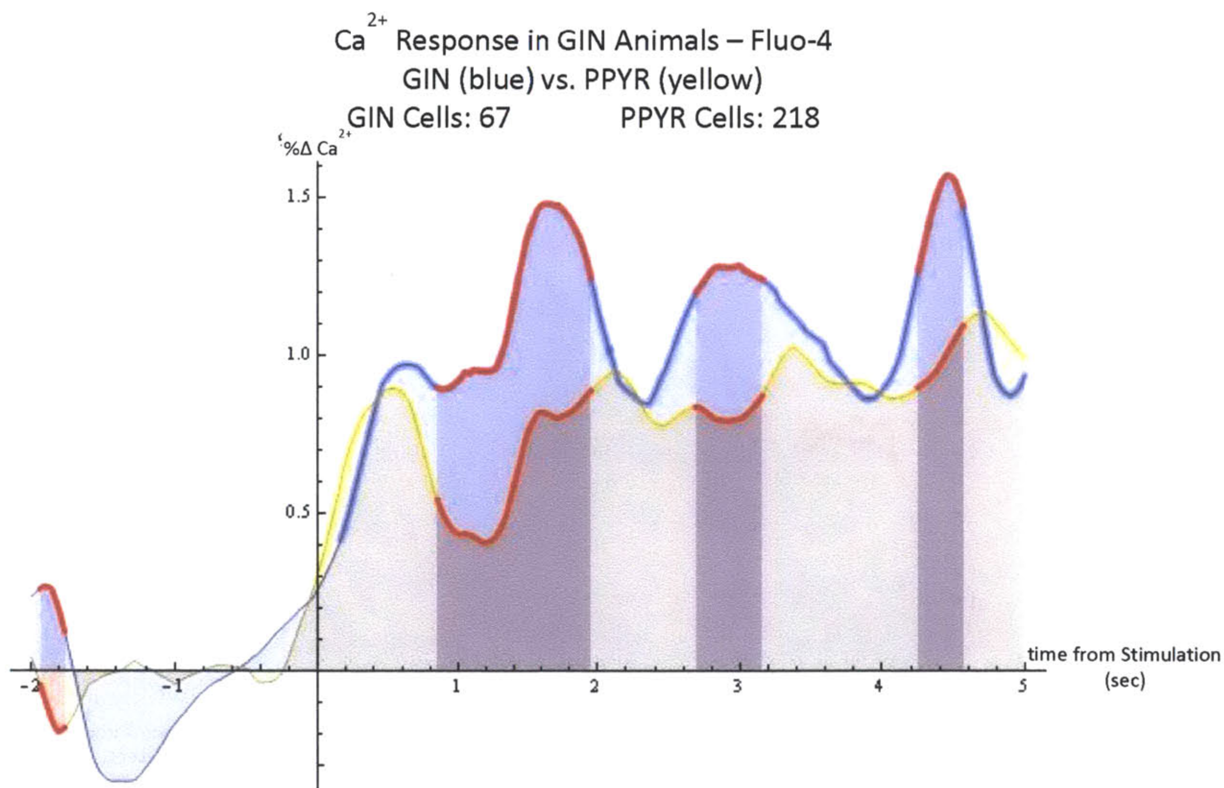

Figure 1-5

Both GIN and non-GIN/putative PYR cells showed a strong initial response to sensory stimulation (artificial whisking) [**Figure 1-5**], with pronounced Ca^{2+} signals rising 0-1 seconds post stimulus onset. This initial response was followed, for GIN and PPYR neurons, by a plateau and significant diminution, respectively, for a period of approximately

a half-second and then followed by a second response peak 1.5-2 seconds after stimulus onset. Consistent with our predictions—that GIN would show facilitation and PYR adaptation—the ratio of GIN to PPYR activity in the response peak 1.5-2 seconds was significantly higher than during the first response peak (2-way t-test, $p < 0.05$). This finding indicates that there is not only a larger GIN response to initial stimulation than we would have predicted based on other reports claiming they are not activated with vibrissal contact or whisking, there is also an enhanced delayed response, not present in PPYR cells. The GIN response remains significantly raised relative to its initial peak for approximately 1.5 seconds and then recedes to a continuously raised, but lower, level for the course of stimulation. The PPYR response also shows sustained activation over the course of stimulation, but does not show a late peak enhancement.

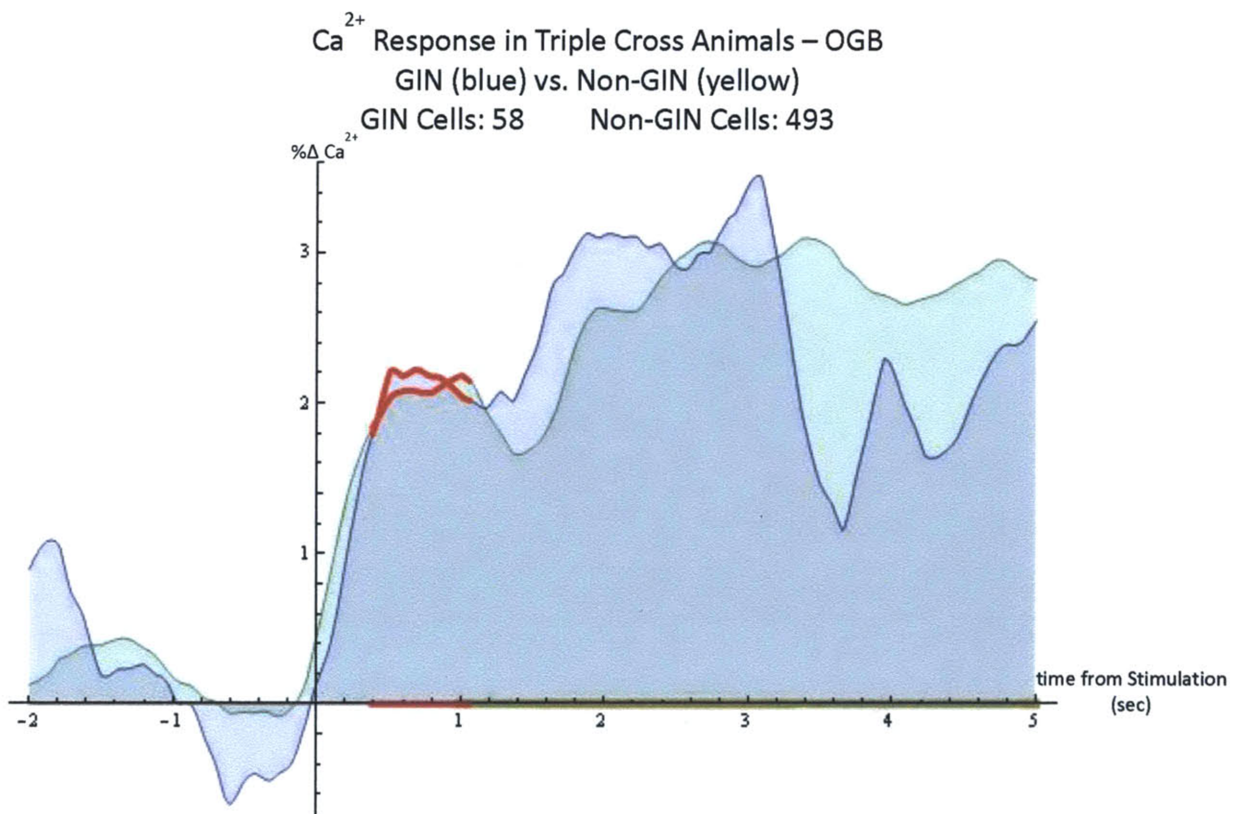

Figure 1-6

A shortcoming of this initial experiment was that close to 15% of our non-GIN sample should, statistically, be IN. The use of an animal with separate markers for GIN and PV neurons (sensitivity and accuracy both >99%) not only adds a second definitively

identified cell type, but also reduces contamination of the PYR population. With this preparation, we directly compared their activity to PV interneurons. The experimental set-up was almost identical to the one previously described with two improvements: We bred a new line of GINxPV-Crextd-Tomato mice that in addition to the eGFP labeled GIN cells had td-Tomato labeled PV cells (cell labeling was both comprehensive and specific {≥99% [Oliva, *et al.* 2004]} and we used OGB as a Ca^{2+} indicator. The reason for the new mouse line is detailed above, the switch to OGB was motivated by two factors. The first motivation was that despite a lower signal to noise ratio than Fluo-4, OGB labels a larger percentage of neurons, an important property given that we wanted to capture as many GIN and PV cells in a single image as possible for direct comparison.

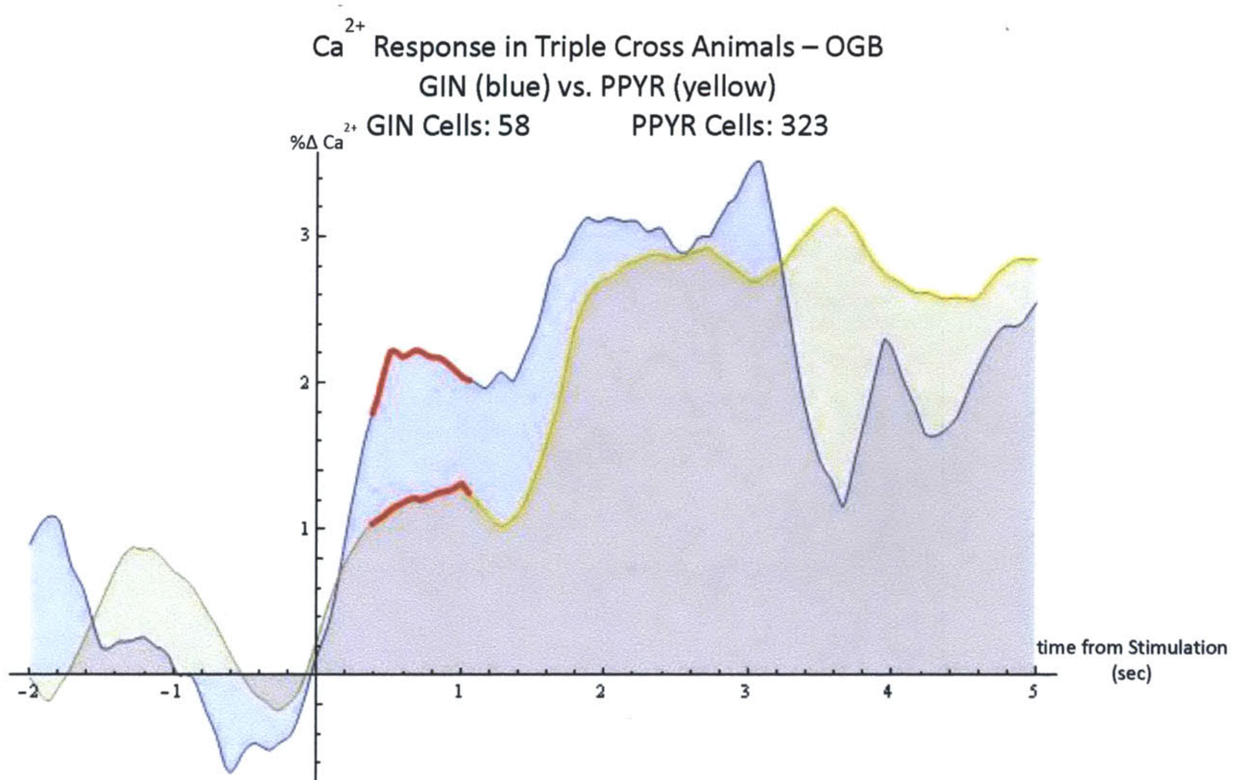

Figure 1-7

The change of mouse lines and Ca^{2+} indicator dyes also served as a means of verifying that our results were neither idiosyncratic to our previous mouse line, as the mouse lines were derived from different background strains (see ***Materials and Methods*** for elaboration), nor were the results a function of any particular quality of Fluo-4, as OGB

has different signal noise properties and a different chemical structure, offering a degree of independent verification of the initial results.

Consistent with our previous experiments, we found that GIN and non-GIN/Putative Pyramidal (PPYR) (also non-PV) cells showed a strong initial response to sensory stimulation (artificial whisking) [**Figure 1-6** & **Figure 1-7**], with pronounced Ca^{2+} signals 0.5-1 seconds post stimulus onset. This initial response was followed, for GIN and PPYR, by a diminution for approximately one second and, as in the previous experiment, a second response peak. In contrast with our previous predictions and experiment, the ratio of GIN (facilitating) to PPYR (adapting) activity in the late onset response peak was not significantly higher in GIN than PPYR.

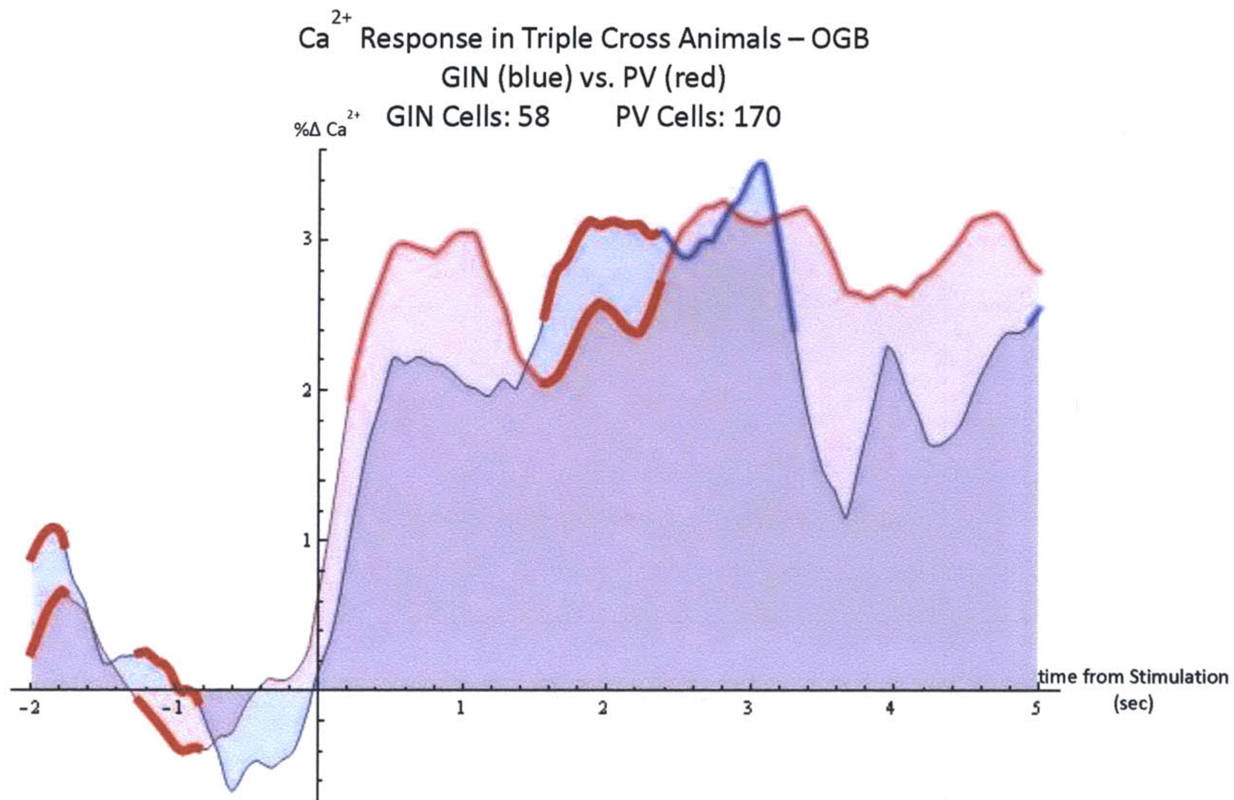

Figure 1-8

The PV neurons' Ca^{2+} signal changes [**Figure 1-8**] differed from GIN and PPYR. While PV also showed an early onset response, this response was significantly stronger than GIN or PYR, consistent with the general observation of enhanced sensitivity in FS

[Swadlow 1989]. Second, PV neurons did not show a "second peak," rather there was a continuous, gradual decrease is Ca^{2+} signal following onset. Those two features suggest the possibility that PV activity may be responsible for the period of interrupted GIN and PPYR firing during the ~1-2 period, between first and second average raw Ca^{2+} peaks. At 1-2 seconds after stimulus onset, GIN responses were significantly greater than PV in this window. This finding is in apparent agreement with their established synaptic dynamics as discussed above.

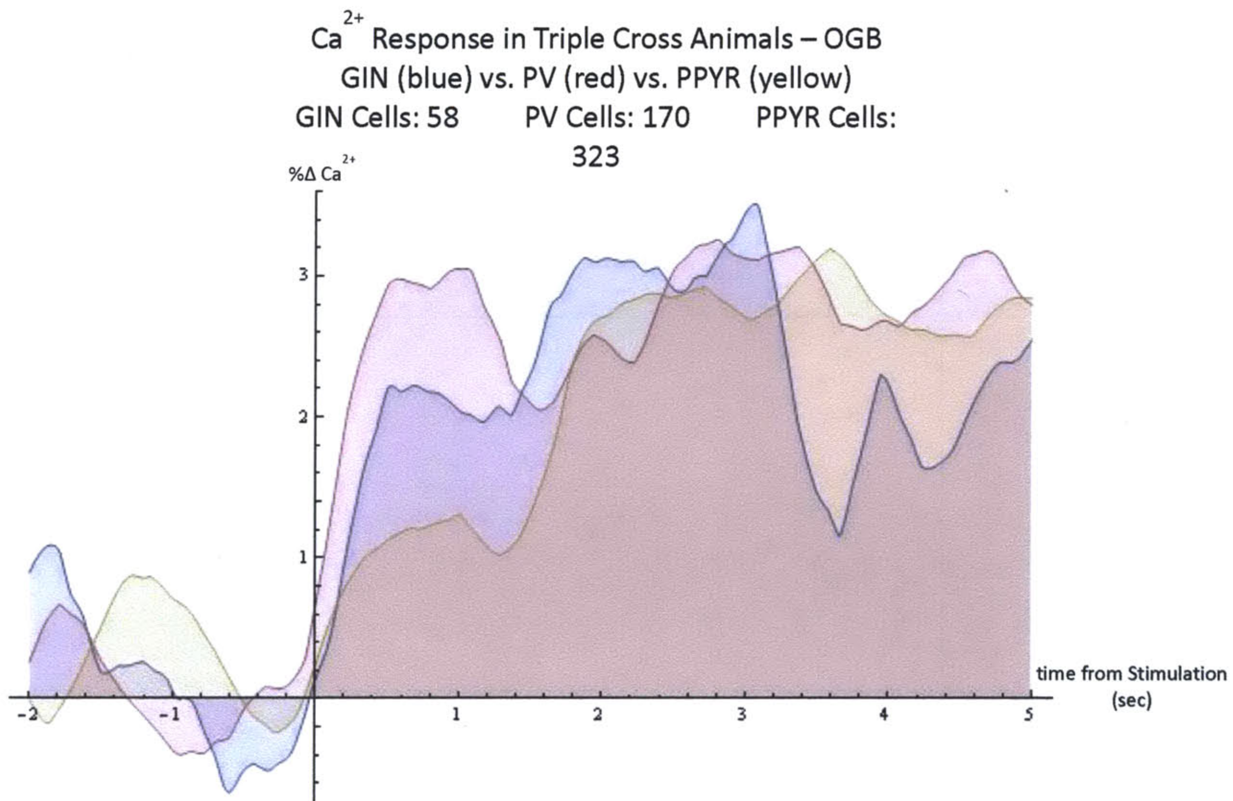

Figure 1-9
(summary figure)

We next analyzed the correlation of Ca^{2+} signals within cells of a given type. **Figure 1-10** and **1-11** show the average within-type correlation among GIN and PPYR neurons from the first experiment, (data smoothed by a sliding 1 second window). Data were normalized to the peak response average of each class. The GIN and PPYR within-type correlation averages were complementary in timing. Average within-type PPYR correlations peaked at 0 to 1 seconds after stimulus onset and then fell to baseline levels, whereas the GIN correlation peaked at 1.5-2 seconds. This peak in correlation corresponds

to the second rise in overall calcium levels observed in the GIN sample. Note that these correlations are not a simple function of overall calcium activity, as GIN cells showed a robust onset response in calcium change, but no similar increase in correlation in that earlier time frame.

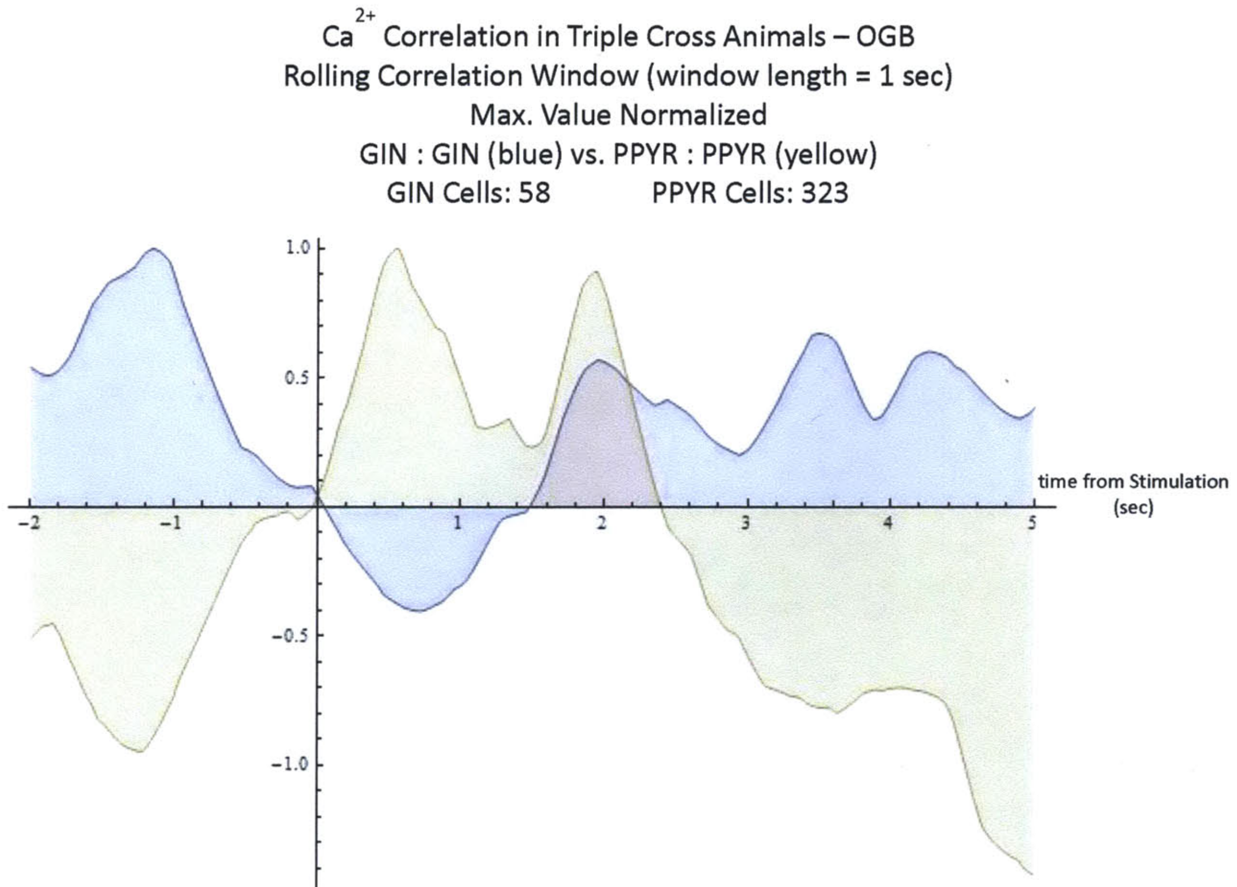

Figure 1-10

In the second experiment, we found the essential findings from our previous experiments repeated [**Figure 1-12**]. GIN and PPYR within-type correlation averages were again complementary. Average within-type PPYR correlations peaked at 0 to 1 seconds and then fell to baseline levels, whereas average within-type GIN correlation peaked during the period that the second peak in the raw Ca^{2+} data occurred. The peaks for GIN and PPYR occurred about a half second earlier in the second data set (possible causes include OGB versus Fluo-4 dynamics and our increased acquisition rate), but the early relative dynamics of GIN and PPYR average within-type correlations were almost unchanged.

Including PV neurons, [also **Figure 1-12**], the average within-type correlation was consistent with the initial analysis of the raw Ca^{2+} data. The peak average correlation of PV neurons overlapped, with slightly longer lags versus PPYR neurons, and ended just as the GIN average within-type correlation began to rise, suggesting that PV neurons may have additional impact (due to both activity and synchronicity) during the period between PPYR and GIN peaks. Like PPYR, PV within-type correlations were almost perfectly complementary to GIN within-type correlation during the first 3+ seconds, with all cell types showing a rise afterward.

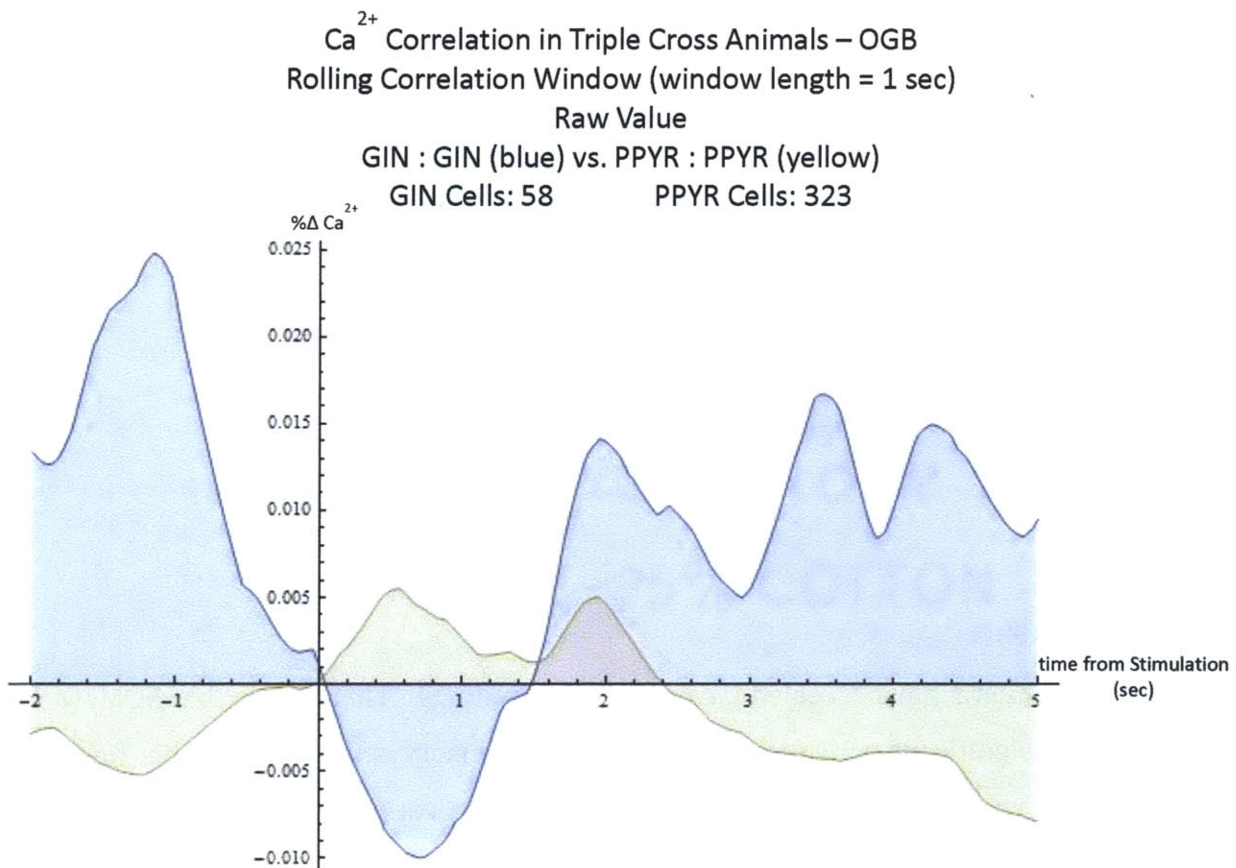

Figure 1-11

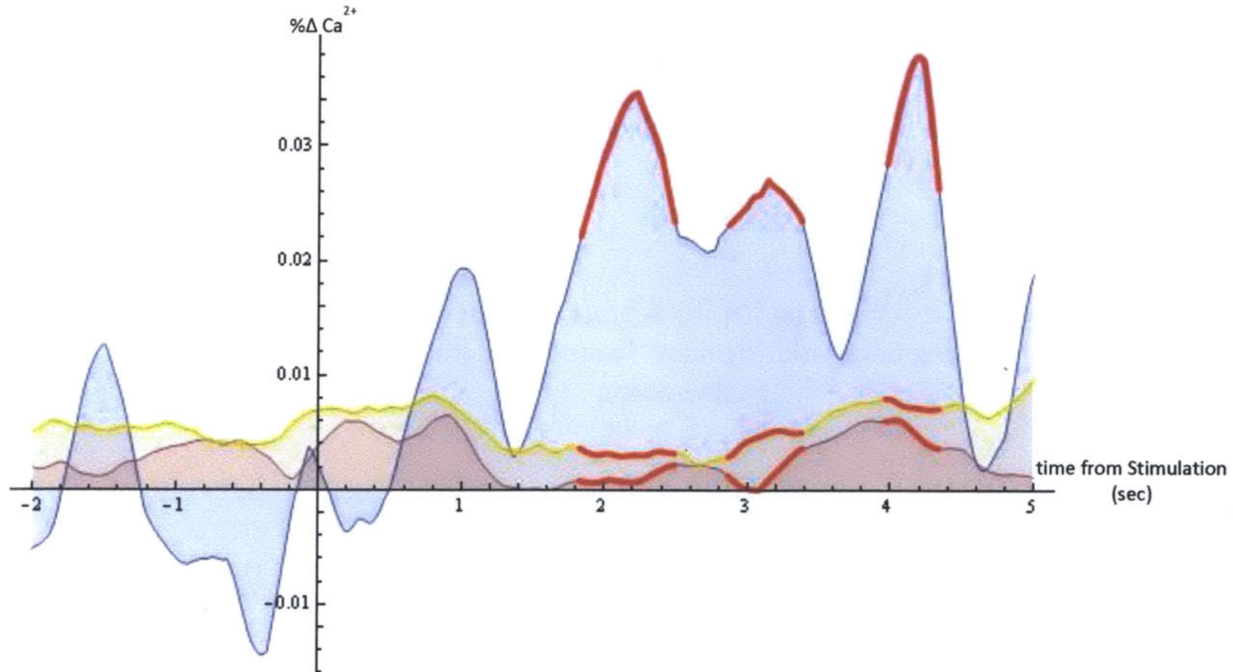

Figure 1-12

1.11 Discussion

Our experiments have revealed two surprising findings. This first is that SOM/GIN neurons showed significant activation at the onset of sensory stimulation. This finding runs counter to *in vivo* findings in Gentet, *et al.* where GIN activation was not present or was abolished immediately following onset of stimulation [Gentet, *et al.* 2011], though it is consistent with work by Hu, *et al.* (2011) showing close synchrony between SOM and fast spiking interneurons. The reasons for these differences are not entirely apparent, however a key difference between our paper and the Gentet, *et al.* and Lee et al. studies (inconsistent) is that our goal was to test whether bottom-up sensory stimulation was sufficient to differentially activate GIN and PPYR networks whereas their papers studied whether behavioral state was sufficient. Our use of both direct electrical control of the

whisker pad an anesthesia both removed the presence of predictive top-down inputs and generally reduced top-down inputs across the board due to the desynchronizing affects of anesthesia. A number of neural correlates (and potential inputs to somatosensory neocortex) may exist across area the brain with spontaneous whisking – motor neocortex in particular coming to mind as there many theories of sensory function posit that it is the difference between motor and sensory information that is ultimately processed and motor neocortex has strong inputs into SI. Follow-up work by Gentet, *et al.* (2012) using optogenetics to directly stimulate somatosensory neurons, thus obviating structured contribution of areas like motor neocortex or the ascending reticular activating system unfortunately only showed the reverse relationship – that SOM activation inhibited pyramidal cells, but did not show what effect pyramidal (or, most importantly, thalamocortical) activation had on the synchrony of different interneuron populations. Notably, neither approach is inherently superior, they simply study the brain at different levels of isolation, with the Genetet and Lee approach giving insight into the activities of SOM and PPYR IN during spontaneous whisking and our work giving insight into the properties of SOM and PPYR IN with regard to their ability to process bottom-up sensory information and thus demonstrating a remarkable ability of those networks to differentiate and selectively respond to minimally processed sensory input.

A second key finding is that SOM/GIN responses facilitate on a multi-second time scale. What is known from *in vitro* experiments suggests that the delayed response of SOM/GIN neurons to continued stimulation, relative to adapting neurons such as PV or PYR neurons, should occur on the order of 100s of milliseconds at most. In contrast, we find delays in the range of thousands of milliseconds. There is only one case where similar long timescale dynamics have been demonstrated in SOM neurons of which we are aware. In thalamocortical slices taken from barrel neocortex of mice, Fanselow (2008) showed that layer 2/3 SOM interneurons demonstrated a delayed response to induced thalamic stimulation that occurred approximately 3 seconds after the thalamic shock and that was sustained for more than 10 seconds. While this finding was not elaborated in that work, it does corroborate our findings that SOM interneurons show long-time scale dynamics in a manner that may better suit them for real-world perceptual problems in some cases than

millisecond scale dynamics only would.

We would not venture to claim a mechanism for the current enhancement, but from what is known about possibly antagonistic PV and SOM networks and the timing of PV activation in both our own experiments presented here, and *in vitro* experiments elsewhere, activity from PV neurons could disrupt SOM network activity. While PV neuron activity may not entirely prevent SOM firing, it would likely at least result in abortive firing and disruption of SOM neuron synchronization as well as the positive feedback loops that would result from said synchronization. This disruption would last at least until such a time as the adaptive mechanisms in PV neurons begin to diminish their inhibitory influence at which point SOM neurons ought to begin to synchronize and facilitate.

These findings *suggest* possible mechanisms by which kinds of computations (such as computations designed for detection of stimulation versus discrimination of stimuli) can occur in a single area of neocortex. Namely, during whisking or regular stimulation, the active interneuron populations are changed, prompting, almost certainly, changes in the network dynamics and thus computations performed in the corresponding local area of neocortex.

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Chapter 2

Fast, Non-Gradual Learning in Neural Network Like Structures With Small Synaptic Weight Changes:

An Exploration of Network Architectures

2.1 Author Contributions

This work is derived from a paper written by myself (Ethan Skowronski-Lutz[1]) and Juyang Weng[2].

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2.2 Abstract

"One-trial learning" is often used as an example of a behavior of biological neural networks that is not or even cannot be displayed by neural network learning algorithms. The general argument stems from an assumption that gradual learning in the network (required by biological evidence for slow rate of weight change at neural synapses) precludes fast qualitative changes in input-output relationships in stable networks. Using networks inspired by the MILN network previously presented by Weng and colleagues we demonstrate "one-trial learning" experimentally and theoretically using a biologically plausible network. The high dimensionality of the network yields qualitative changes in input-output relationships by small changes in representation at successive network layers. We further show evidence that the dimensionality of the signal's representation may be key to balancing robustness with speed of learning.

2.3 Introduction

The development of "neural network " learning algorithms opened a broad spectrum of problems and solutions to function estimation and machine learning, however, despite the original biological motivation of neural network algorithms they have fallen into disfavor as a method of studying neural and cognitive function [McCleland, *et al.* 1995]. The reason for this disfavor is multifarious; two broad and important classes of critique in this vein however are (1) existing neural network algorithms are biologically implausible (2) existing neural network learning algorithms do not or *cannot* show various behaviors observed in animal physiology of behavior.

I feel that these critiques are incorrect and the misperception to the contrary unnecessarily removes an important, perhaps key, tool in the quest to understanding biological learning and particularly neural learning. I would like to join others in addressing these concerns concretely and do so here by presenting a previously described biologically plausible neural network learning algorithm (Multi-layer In-place Learning Network, MILN) [Weng, *et al.* 2007] and offering both experimental evidence and theoretical proof that it can display "one-trial learning" with biologically plausible bounds on changes of synaptic weights without repeated internal training.

"One-trial learning", the broadly defined ability of animals/biological neural networks to appropriately represent/classify new input patterns after a single presentation and with near zero delay, is a common and critical behavior in animals/biological neural networks. One trial learning is, in most cases, phenomenologically defined. That is to say the neural mechanisms that mediate fast learning without otherwise disrupting animal behavior are unknown [Hulme, *et al.* 1991; Maquet, *et al.* 2007; McClelland, *et al.* 1995]. Nonetheless, one-trial learning is commonly used as an example of how neural network learning algorithms fail to emulate biological neural networks [Hulme, *et al.* 1991; Maquet, *et al.* 2007;] and is often presented as an unachievable behavior for biologically plausible neural networks [Hulme, *et al.* 1991]. As best I understand, the argument against one-trial learning by neural network learning algorithms stems from: (1) The historical association of neural network learning algorithms and back-propagation or other gradient-descent across an error/energy landscape methods of neural network update (e.g. [McClelland, *et al.* 1995; Weng, *et al.* 2007]) and the implication that network behavior changes in a slow, gradual manner. (2) The biological plausibility constraint imposed by small maximum changes in synaptic "weight" as a function of time (or "update"). Again, with the implication that network behavior can only change gradually over time. (3) The observation that most neural networks have not demonstrated one-trial learning behavior (without instability) and presumably therefore cannot.

The above arguments, while reasonable, are insufficient: (1) Not all neural networks use gradient-descent learning methods and certainly not all use back-propagation. MILN, for example, explicitly eschews gradient-descent learning as biologically implausible [Weng, *et al.* 2007] due to the nature of calculations involved. More broadly, movement along an energy or error surface, buy means of gradient descent or otherwise, does not imply a constant rate of movement along that surface. Neural network learning algorithms are generally function approximates and move through a space of simulated functions where small movements can yield qualitatively different behavior, especially when the space is high-dimensional [5]. (2) Biological constraints on the rate of synaptic weight change are of key importance, however (a) most neural network learning algorithms output is *not* a linear function of the synapses—non-linear functions such as thresholding and lateral-inhibition mechanisms can yield large changes in output for modest changes in weight of input (b) because many networks contain a large number of synapses small changes at any individual synapse are not necessarily limiting—in particular changes to sequential synapses, even in a simplified linear system, multiply together rather than sum. (4) Our motivating counter-point is that the brain *is* a neural network of some sort providing its own counterexample; however we hope that the following work provides additional counterexamples.

2.4 General Methods

Using supervised or unsupervised learning by presenting (x_i, y_i) pairs, i=1, 2, ... k where k is some 'large' number (e.g. $k = 10^6$) such that $y_i = f[x_i]$. Given a new sample $(X_{(k+1)}, Y_{(k+1)})$ our goal is to show that $y_i=f'[x_i]$, i= 1, 2, ... k, k+1. Where f' si updated from f using the regular MILN learning rule that changes only weight of the best matched weight vector in every layer by a small amount and does not otherwise damage the memory for the first k samples.

This work is exploratory in its nature and as such it utilizes multiple network architectures to investigate one-trial learning in artificial neural networks. Common to all networks I that they are composed of neurons (**X**) in layers (**L**), (X_i *within* L_j). Each

neuron takes n inputs ($X = (x_1, x_2, \ldots, x_n)$ and is defined by n weights $X = (w_1, w_2, \ldots, w_n)$ corresponding to the n neurons composing the previous layer or the number of nodes representing the initial network input.

In MILN activation reflects the multiplication fo presynaptic discharge by a weight-like function defining synaptic transmission. Represented computationally as $y = g(w1\ x1 + w2\ x2 + \ldots + wn\ xn)$, where g is a nonlinear sigmoidal function, taking into account under-saturation transition, and over-saturation appropriate to a general description of neural activity [14]. For this work however, I have shed some degree of biological verisimilitude in favor of simplicity of expression with the intention of exploring the space of models more quickly and then returning to greater biological plausibility after such an exploration. Thus, the above only applies to the first networks presented. For most of the networks below instead activation of y is represented by $y = T(\ 1 - (|w1\text{-}x1| + |w2\text{-}x2|+\ldots+|wn\text{-}xn|)/H)$, where H bounds the value of y such that it must lie within the range of [0,1] in the Real numbers and T passes the calculated value or 0 depending on various parameters.

Activation here, then, is essentially a distance function calculating the distance of the input from the weights defining neuron X. The general validity of this calculation stems from the assumptions that the total value of any neurons' input weights are normalized to some factor, consistent with experimental and theoretical work on homeostatic plasticity and excitation/inhibition dynamics in real networks [Carr & Konishi 1990; Cook & McReynolds 1998; Turrigiano 1999; Weng, *et al.* 2007]. It is also very similar to the form that MILN calculations ultimately take; that network's computations are explained in full in [Weng, *et al.* 2007].

In the cases explored here H takes one of two forms. In the case of whole-network normalization H is equal to the largest distance of any neuron in a layer from the input. In the case of local-network normalization H is the largest distance of any neuron in a local region about a X (e.g. the n-closest neurons).

The motivation for this approach stemmed in part from a hope that for local normalization the activation would exhibit an exponential-like fall-off based on the assumption that distance would increase by large amounts, but differential distance would be roughly equal leading to an activation curve by distance much like the following. (Unfortunately, most networks did not yield such a nice curve as seen in the results section; however this may be due in part to the small size of the networks).

T acts as a threshold function that either passes the calculated value or changes it to 0. Here we explore use of T to pass values based on their activity relative to global or local activity. Specifically, we employ either the global top-k method employed by MILN network, where only the k most active neurons pass their values to the next layer as input or a variant local top-k method where the k most active neurons with a local cluster pass their input to the next layer.

One of the key goals (though it is not entirely me here) is to distribute the weight changes associated with learning across many neurons when the input(s) are not well represented by a small number of neurons in order to allow both high plasticity and maintain stability. Theoretically, the ideal network would only have k active neurons, where k is proportionate to how poorly represented the input is in the network and those k neurons would maximize the averaged representation of the input (weighted for activation) across the active neurons, minimizing redundancy and maximizing similarity. This would not only have the advantage of expressing novel inputs in higher-dimensional spaces, with the nodes themselves representing both common inputs and the basis vectors for more complex representations. It would also allow weighted memory, due to the decreased plasticity for inputs with sparser representations, allowing us to eschew an explicitly running total of the past activity of each neuron.

In practice, however, none of the networks below achieve properties quite like the described ideal, but do approach it to varying degrees and provide an excellent fist5 pass

exploration of the advantages and trade-offs associated with variably-sparse representation.

2.5 Experimental Results

Network 1 | Explicit excitation & Inhibition in a MILN-like Network Computational Architecture

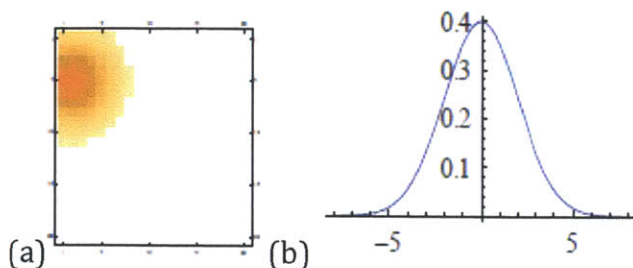
Multi-Layered Network modeled off of MLN. The initial weights are set to provide a 2D Gaussian excitatory receptive field for each neuron. Initial activation of each node is computed as for the MLN network (described above).

Prior to sending output to the following layer, however, a second calculation is made for each node based on the surrounding activity. Each node is provided with a mostly inhibitory receptive field, modeled as the difference of two 2D Gaussians, modeling an inhibitory receptive field. The lateral activation is calculated the same way as for feed-forward activation, with the two activations summing to produce the layer's output.

Unfortunately, while I explored a variety of algorithms for balancing excitation and inhibition (some of which were promising) the excitation/inhibition variant networks tended to require hand-tuned balancing, which became a problem during learning.

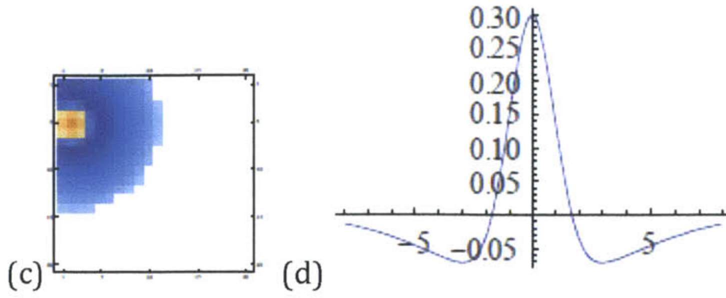
At network initiation activity was well balanced and would quickly find a stable equilibrium. However, learning rules caused unpredictable changes, that could result in instability of the network (e.g. epileptiform activity or zero activity).

Figure 1



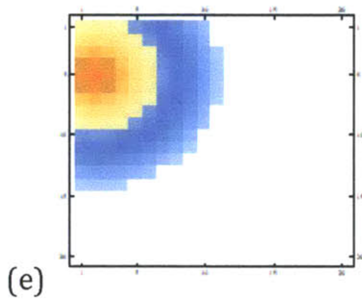
(a) 2D Gaussian Excitatory Receptive Field for a Sample neuron

(b) Example 1D Gaussian Distribution



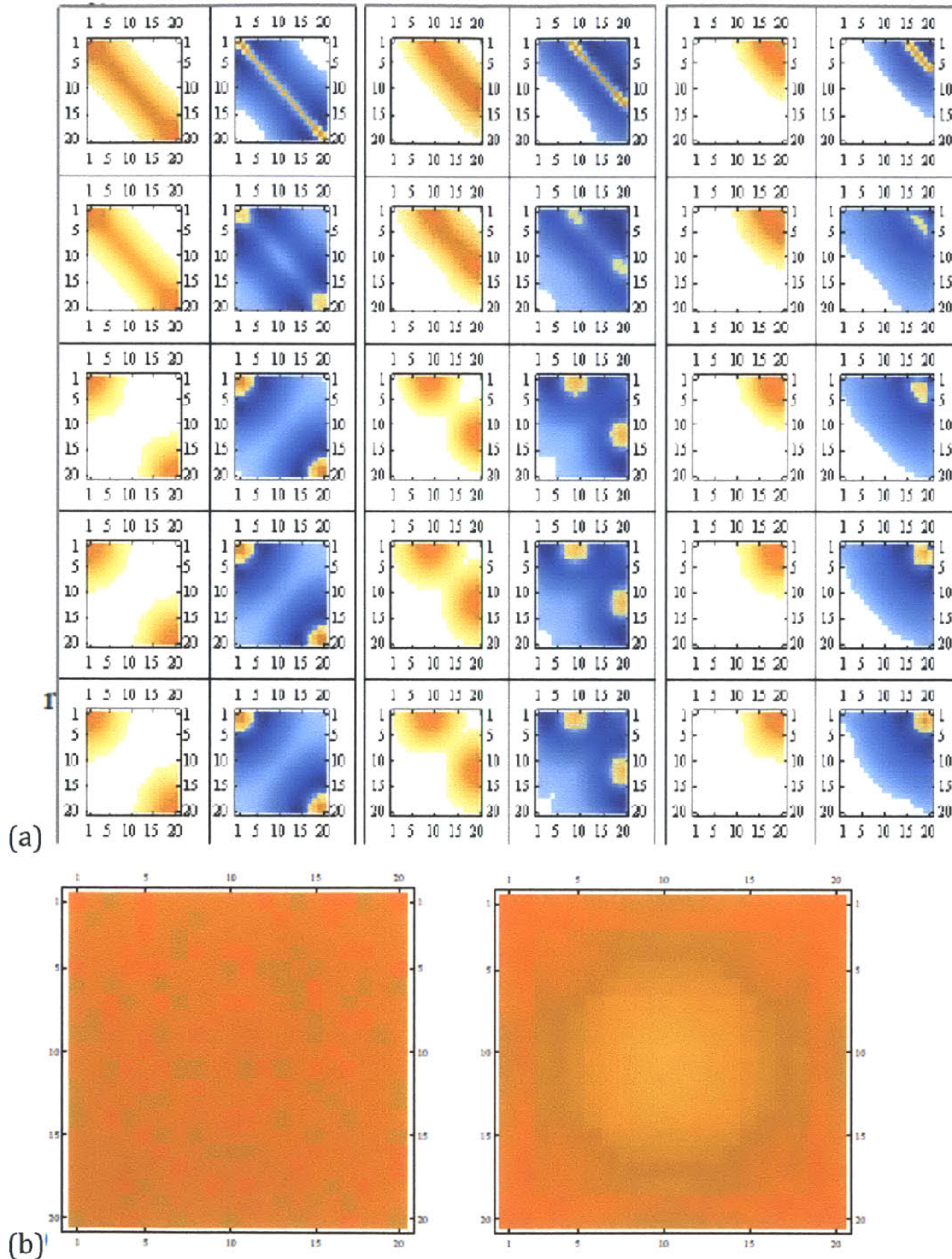
(c) 2D Difference of Gaussians Inhibitory Receptive Field for a Sample Neuron

(d) Example 1D Difference of Gaussians Distribution



(e) Sum of Excitatory & Inhibitory Receptive fields for

Figure 2

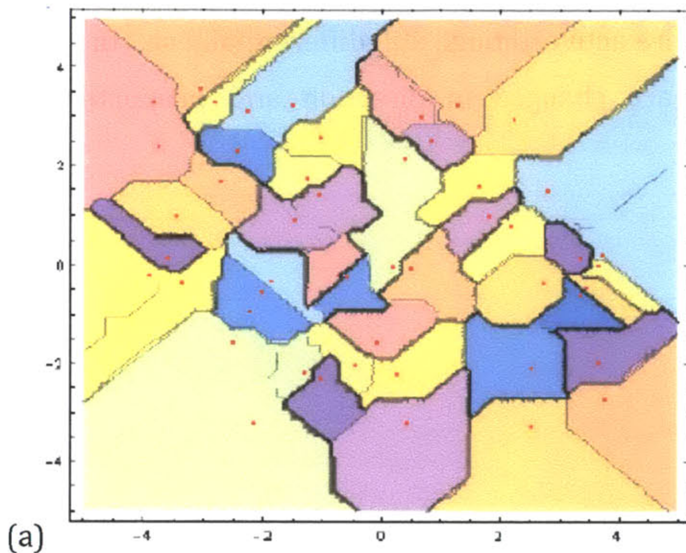


(a) Examples of Stabilization of Banded Inputs Shortly After network Initialization

(b) Examples of Unusable Outputs that Can be Generated

Network 2 | Distance Network Implementing Global Top-K Computational Architecture: Multi-layered network with activation based on the globally normalized distance described above.

Figure 3



(a)

(a) 2-D Slice, Proximity Region Graph

In each layer only the activity of the k most active neurons in a layer are used as input for the succeeding layer. Activity is determined by proximity (L1 norm) of the input to neurons if both are represented as points in n-dimensional space.

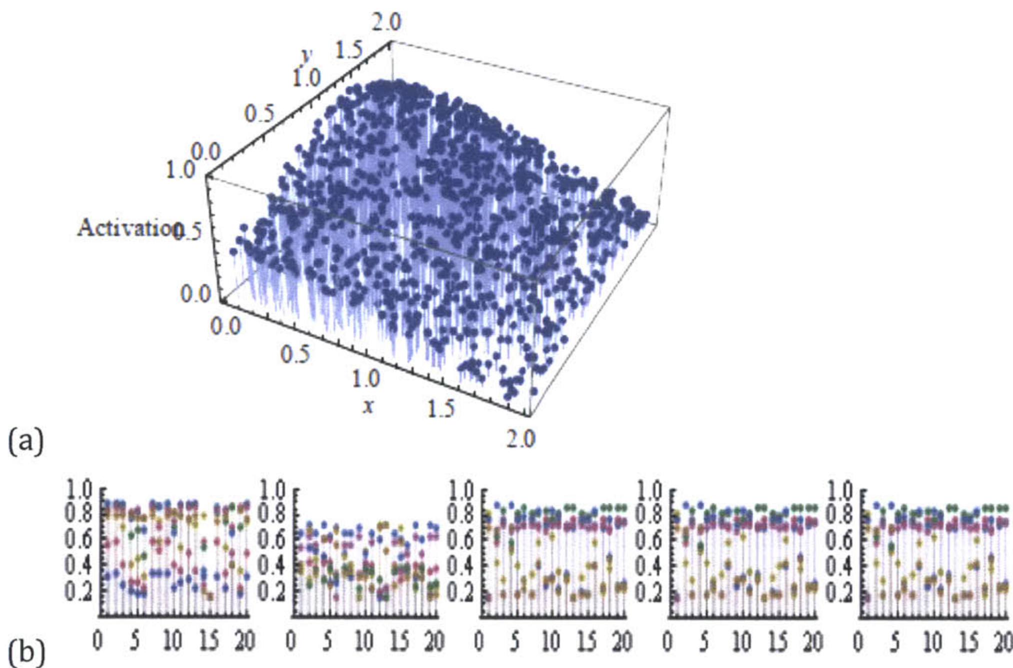
Due to the sparse input of each layer the above architecture is *highly* efficient from a computational time perspective. It also demonstrates an ability to rapidly modulate the output as a function of the input. Unfortunately, when k is low the learning speed/robustness trade-off is high. This is presumably a result of two separate problems: (1) All weight changes must be channeled through the small number of active neurons. The weight changes are restricted to the input dimensions corresponding to the previous k active neurons however this still means that similar, but different inputs are highly sensitive to each other and makes the learning of arbitrary divisions between input

patterns somewhat difficult. (2) The k active neurons are often very similar to each other and as such capture redundant structure of the input.

Network 3 | Fully Active Distance Network Implementing Global Normalization Computational Architecture:

This network is the same as network 2 where k = the number of neurons in a layer. One approach to dealing with the above trade-offs in a top-k selection process is to maximize k. By maximizing k all neurons are active, though still differentially so. In order to maintain selective learning weights are changed in direction and proportion to activation (which ranges from [0,1]).

Figure 4



(a) Gradient of activity Calculated by the L1 Norm Distance Function Between Input and Each Neuron.

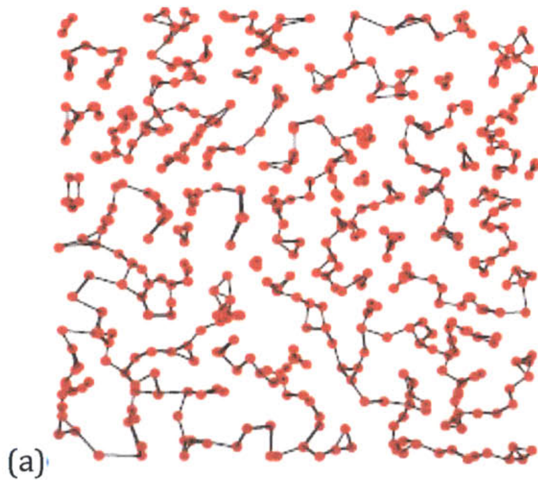
Note the difference between this and the above concept of distance (which is a nearest neighbor approach).

(b) Sorting of Separate Inputs into different activity patterns. Presentation number increases horizontally.

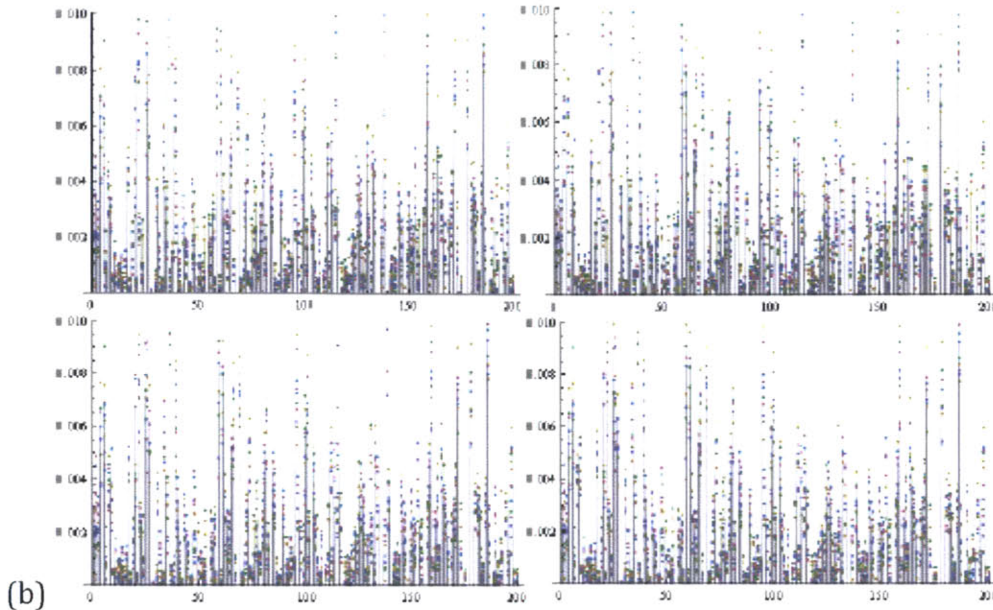
Network 4 | Fully Active Distance Network Implementing Local Normalization Computational Architecture:

Network 4 is identical to network 3 with the exception that activity is normalized based on the raw activity of a neuron's n-nearest neighbors (determined using the L1 norm distance between neurons' input weights). The local normalization provides two advantages over the previous network: (1) It penalizes redundancy by normalizing within a group of similar neurons, thereby promoting multiple 'views' of the input and potentially more plasticity. (2) It avoids the problem of a single outlier driving the majority of neurons towards maximum activity, which sometimes occurred in network 3.

Figure 5



(a)



(a) An Example of 2D 4-Nearest Neighbor Connected Graph. The structure of the graph illustrates the sort of locality used in network 4.
(b) Stability of Input Representations in the Terminal Layer of a Network 4-type Graph. Presentation number increases along the horizontal with each graph. Within each graph the x-axis denotes the activation of a specific node, and the colored points represent the activation for different inputs. Note that the gross structure of the graph is table, despite a high degree of variability between inputs—a very desirable property of the network.

Network 4 shows a much greater degree of stability than network 4 and also shows rapid adjustment when new inputs are presented. Computationally, however, network 4 is roughly an order of magnitude less time-efficient than network 3, requiring fewer nodes in order to maintain similar throughput rates.

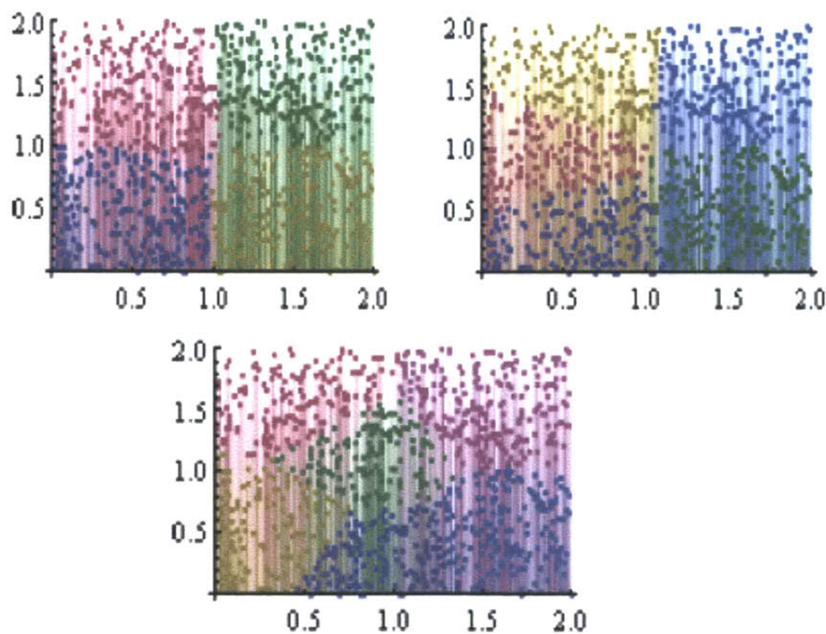
Network 5 | Distance Network Implementing Global Normalization and Local Top—K Computational Architecture:

In an attempt to balance the benefits of top-k (high-efficiency) with the flexibility and relative robustness of the local distance normalization network local top-k only passes the k-most active neurons' responses as input to the subsequent layer. Unlike Global top-k local top-k selects only the single most active neuron from k distance-clustered neurons in

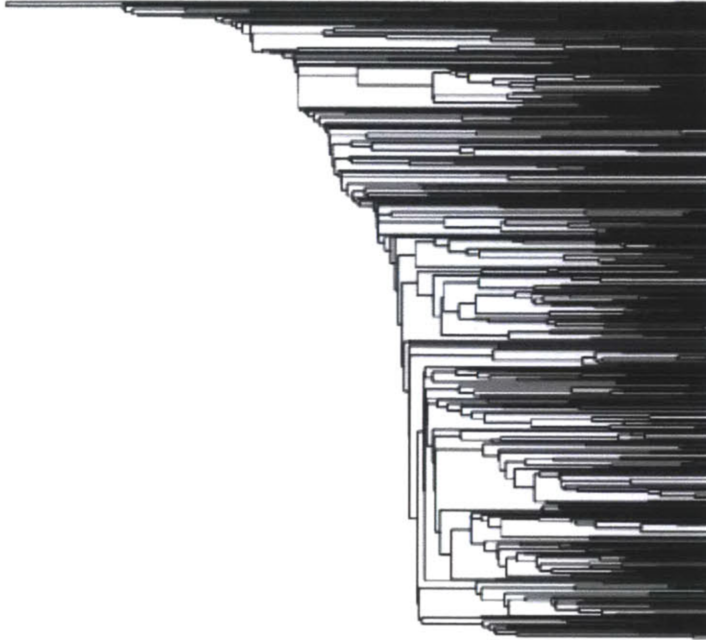
the hope of minimizing redundancy. Also unlike Global top-k, the local top-k network sets k to be proportionate to the maximum activation—resulting in more neurons coding for the input when the input is more poorly represented.

The network is both robust and able to learn new inputs quickly; however, different algorithms yield very different results, especially at low k. This is presumably because at low-k any given cluster is more likely to border another, potentially allowing the selected neurons to actually lie very near one another, in contrast to our original desire.

Figure 6



(a)



(b)

(a) An example f local top-k for k= 4, 5, &6. The individual neurons are clustered into groups according to their similarity (there are a variety of clustering algorithms, the specifics of which are beyond the current scope of this discussion).

(b) Truncated Dendrogram Plot. This gives an example of clustering based on recursive rules, where clusters are made by iterative combination of single elements (clusters or points). The result is a map of increasingly homogeneous clusters that allow for rules based selection of the fragmentation and similarity of clusters used when choosing what groups should act as the basis for local top-k selections.

2.6 Major Setbacks

As is clear from the results section, the work currently being presented is preliminary and exploratory. While the investigation of multiple neural network algorithms has been highly instructive, in particular to me personally, a rigorous comparison between methods is no practical at this point. There are a number of reasons for this including the relatively low computational efficiency of some of the algorithm. This is presumably a factor of my own imperfect implementation and of the fact that none of the above algorithms have been compiled for faster execution. Besides that, and part of the

cause of that, is the fact that the 5 networks discussed above are really descriptions of general classes that were explored in the course of this research. Each network, in the course of this work, was actually implemented as dozens of variants employing different update rules, distance metrics, inputs/output spaces, etc. Finally, one of the most glaring difficulties was defining "learning" and "stability". In practice this was usually defined by the degree of change in network response for a given input after x number of updates. However, hysteresis, choice of training examples and similar concerns made rigorous analysis of either stability difficult. Rigorous numerical approaches could be taken but were ultimately untenable here due to the multiplicity of architectures employed. Stability analysis were compounded by the difficulty of defining "learning".

One measure of learning was convergence of the output on a stable representation of a new input, however the actual metric should be differentiability, which must be classified according to how the network takes inputs. Clustering output responses provided a useful measure of response similarity, however, as was illustrated anecdotally many times during my research, determinability does not increase linearly with distance, but depends critically on state of the network and the rules governing it's update. Nonetheless, distance, or dissimilarity, metrics were useful rough measures of categorization, however validation of that categorization scheme should come from directed learning experiments where the importance of output class on re-categorization and generalization can be better assessed.

2.7 Conclusions

Neural-like Networks, even when bound by small changes to synaptic weights are clearly able to change their weights quickly and dramatically in response to single presentations of data. Biological evidence indicates that they can do so while retaining robustness a result that is also suggested by the research above, however the computational space that we can explore is vast and there are many ill-behaved networks that oscillate wildly or converge to a single point regardless the input.

My research has pointed to two important ideas however. The first is that he amount of excitation characterizing a network may be proportional to the novelty or ill-representation of a stimulus in that network, using the recruitment of more neural resources to represent the input in a higher-dimensional space, with more strongly represented (and statistically common) inputs as basis vectors. There is a combinatorial increase in the number of possible codes as the number of active nodes is increased, even for simple on/off descriptions of neural behavior. It is computationally likely that this is taken advantage of in the brain, and indeed systems neuroscience studies indicate this to be the case [Miller & Desimone 1994; Skaggs, *et al.* 1998; Stickgold, *et al.* 2001] though no strong computational reason has been put forth before. The other important concept my research has pointed to is the criticality of the co-regulation of activation inhibition dynamics. STDP and Hebbian rules may provide reactivity accurate descriptions of synaptic updating for excitatory synapses, but it is much less clear how inhibitory synapse weights are apportioned, despite their known plasticity [Carr & Konishi 1990; Zilles, *et al.* 1998]. It is theoretically possible that most synaptic dynamics concern excitation and that inhibition is relativity static and Dependent on careful modulation of excitatory synapses, but this seems unlikely and appears to be experimentally implausible [Carr & Konishi 1990; Cook & McReynolds 1998; Zilles, *et al.* 1998].

It is my strong suspicion that the excitatory inhibitory dynamic balance is also key to network robustness in the face of or one-shot learning. While I do not have sufficient evidence to make a strong case for this fact yet, the explorations I have undertaken of different neural architectures with both explicit and implicit representations of excitatory/inhibitory dynamics have enabled me to begin developing key intuitions provide an excellent starting point from which to continue this study until concrete conclusions can be drawn and more light shed on the computational mechanisms of fast robust learning in biological neural networks.

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Chapter 3

The Role of Advanced Neural Maturation in Autistic Pathology

3.1 Author Contributions

This work is derived from a paper written by myself (Ethan Skowronski-Lutz[1]).

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3.2 Abstract

Autism is a common and increasingly diagnosed developmental disorder with of unknown etiology [Gillberg & Coleman 1992; Rapin 1994; Schopler 1994; Croen, *et al.* 2002; Blaxil, *et al.* 2003]. Diagnostic criteria for autism are purely behavioral, clinically defined by insistence on sameness, lack of normal socialization/relation to others, and delayed language acquisition [Wing & Gould 1979; Gillberg & Coleman 1992; Rapin 1994; Sigman 1994]. Non-diagnostic characteristics include by impaired "abstract" thinking, impaired ability to generalize learned information, repetitive/ritualistic behavior, as well as psychophysical and widespread neuro- anatomical,[Bauman & Kemper 1994; Schopler 1994; Piven, *et al.* 1995, 1996; Bailey, *et al.* 1998; Kemper & Bauman 1998, 1999; Hardan, *et al.* 2000; Courchesne, *et al.* 2001; Aylward, *et al.* 2002; Sparks, *et al.* 2002; Bigler, *et al.* 2003; Lainhart 2003; Herbert, *et al.* 2003, 2004; Tsatsanis, *et al.* 2003] architectonic,[Bauman & Kemper 1994; Kemper & Bauman 1998; Casanova, *et al.* 2002] chemical,[Anderson 1994; Minshew 1994; Friedman, *et al.* 2003] and recorded brain activity,[Johnson & Ross 1994; Schultz, *et al.* 2000; Allen & Courchesne 2001, 2003; Grice, *et al.* 2001; Pierce, *et al.* 2001] abnormalities. Autism Spectrum Disorder (ASD) encompasses autism and other disorders that share very similar "core deficits" but that do not necessarily meet the criteria for autism (e.g. Asperger's syndrome, Williams's syndrome, and pervasive developmental disorder (PDD)). Behavioral profiles of persons with ASD can vary widely (as it can "autism") with differing degrees of severity of the diagnostic criteria and including persons with severe mental retardation and genius level IQs [Waterhouse 1994]. Primarily because of that and poorly understood non-Mendelian pattern of inheritance, variable symptom profiles, and pervasive nature of the disorder many have suggested that autism actually encompasses multiple etiologically distinct disorders, however some theoretical research focused on the developmental nature of

autism has attempted to find coherent etiological mechanisms to account for autism and other ASD disorders [Cohen 1994; Gustafsson 1997; McClelland 2000].

3.3 Introduction

It has already been suggested that the widespread nature of ASD deficits (on cognitive and biological levels) may be a result of early deviation(s) in brain development altering the context otherwise normal developmental mechanisms are expressed in [Allen & Courchesne 2003; Gage, *et al.* 2003]. In particular, recent studies have pointed to anomalous brain growth patterns, localized particularly to white matter tracts, that may occur prior to any other diagnosable autistic criteria as possibly being common to all autistic and thus perhaps fundamental to autistic etiology [Aylward, *et al.* 2002; Courchesne, *et al.* 2003; Akshoomoff, *et al.* 2004]. Very little theoretical work has focused on how observed early life patterns of abnormal growth may alter developmental trajectories in otherwise healthy humans. Fortunately, work on the importance of maturational synchrony during development has recently gained interest in some areas of study and may provide a clues as to how brain growth anomalies and other autistic deficits interrelate.

3.4 Generalization & Immaturity

Maturation is generally regarded as a process of improvement whereby traits that would be detrimental in an adult (e.g. unfused bones in the skull) are replaced by traits more adaptive in an adult. That approach overlooks the potentially important fact that in most organisms there is relatively consistent co-maturation of traits; their adaptive value may be greater in a specific (immature) context. For instance, the timing of fusion of the plates in a human skull is opportunely coincident with a significant decrease in the rate of neuronal maturation and glial proliferation, both responsible for significant increases in brain volume in early life [Baumann & Pham-Dinh 2001; Bourgeois, *et al.* 2001; Neville & Bavelier 2001]. The immature context is also frequently marked by naïveté on the part of the immature organism with regard to various conceptual modalities (e.g. lack of

geographic knowledge, lack of motor knowledge—how to walk, etc.), and may also be synchronized with other immaturities in a synergistic fashion.

Turkewitz and Kenny (1982) point out that immaturity in the nervous system may be adaptive for a naïve animal both by limiting potentially self-hazardous actions and by facilitating learning through systematic simplification of input. [Turkewitz & Kenny 1982] We may readily accept the former; motor system immaturity, for example, may be adaptive by preventing a naïve animal from wandering away from its mother. The later is probably more surprising. Turkewitz and Kenny proposed as an example that the problem of size constancy (disambiguating changes in the size of an objects' retinal projection due to distance from changes in the object's form) may be ameliorated by severe restriction in the (human) infant's depth of visual field. Limitations to depth of visual field result in commensurate limitations to the range of size variation attributable to viewing distance potentially disambiguating other relationships provided by visual input. The progressive increase in depth of field that occurs during maturation might also facilitate the learning of size constancy itself by allowing the system to establish relative object sizes first as a framework for a broader theory of object identity and then size constancy latter. This is supported by reports that in humans evidence of a theory of size constancy is initially only seen for objects close to the infants and would be further supported if that the distance at which size constancy is evidenced proves to increase more quickly than depth-of field (implying that 'principles' of size constancy may have been generalized rather than relearned at different depths of field) [McKenzie, *et al.* 1980].

Newport (1988, 1990) used the same concept, which she dubbed the "less is more" hypothesis, to account for differences in the types of errors committed by speakers who learned a language before or after a "critical window" in language acquisition [Newport 1988, 1990]. Briefly: she suggested that increased working memory (or some other learning "resource") for mature speakers might complicate mapping of form-meaning relationships in the new language because of the larger "search space" available [Newport 1988]. Mature learners' (non-native speakers') errors consist heavily of incorrect or inappropriate morphologies (which would probably be derived from form-meaning

mappings) whereas young speakers show better mastery over morphology, but make more errors of omission—as we might expect given their reduced working memory [Newport 1990]. The theory that reduced learning resources (relative to some 'mature' state) can facilitate language learning is supported by research into recurrent neural networks by Elman (1993). Elman demonstrated that for a simple recurrent network exposed to a stimulus with a grammar-like structure learning could be made more efficient (and in some cases was only possible) when network size was reduced relative to the size necessary to accurately represent the grammatical structures and then iteratively increased—observations that have been supported by continued research in the same vein [Kirby & Hurford 1997]. When the naïve networks began at a 'mature' size they were unable to learn compels grammatical structure. Elman bears special responsibility for examining the principles behind the phenomenon of facilitated learning through "iterative" or "incremental" increases in input complexity (a feat that can sometimes be accomplished by handicapping the learning system—e.g. decreasing the size of "hidden units" within the recurrent networks effectively decreased working memory, only allowing the system to analyze local grammatical relationships) [Elman 1993].

Neural networks, rather than formulating simple statistical correlation tables, appear to 'extract' relationships from the data they are given, but do so in an incremental manner—the network's representation of data relationships at one point must bear a certain resemblance to the network's representation of data relationships at a prior point, a function of the learning rules used to modify inter-nodal weights. If the network represents the data relationships in a manner significantly different from some 'ideal' solution (for that network) then the difficulty of finding the ideal solution will become that much more difficult. Simplification of the data in a way that reduces noise or allows the disambiguation of certain relationships can prevent early erroneous representations from significantly biasing future solutions. The inter-nodal weights are also more malleable because of a sigmoidal relationship between input to a node and output from a node. After exposure to data the absolute value of the inter-nodal weights tends to increase, so the potential change in synaptic strengths is reduced for a given amount of error in an activity iteration.

Processing handicaps can constrain input to a learning system in a way that actually highlights certain relationships, facilitating the learning of those relationships and subsequently others by disambiguating their representation in the learning system. Robotics has seen increasing use of ambulatory constraints to aide in motor learning recently [Lungarella & Berthouze 2003; Cho, In Press]. And the importance of past experience in shaping and channeling future experience is becoming an important part of theoretical understanding of development and learning, especially in the wake of connectionist popularity [Kuhl 2001]. Recalling the significant glial proliferation and neuronal maturation mentioned earlier: besides reducing head size at birth (allowing for a narrower and more stable female pelvis—important to erect human posture), allowing contextually directed neural development (rather than genetically hardwiring detailed neural architecture), and reducing unnecessary time *in utero* it may also provide adaptive neural processing constraints. Variations in the time course of either, as is strongly suggested by recent findings in young persons with ASD, could be potential sources of learning-related pathologies.

3.5 Brain Growth Anomaly

White matter abnormalities in autism consist of an apparent acceleration of the normal course of white matter development; including accelerated proliferation early in life followed by minor regression later in life. At birth head size in autistics appears normal, but by roughly 2-3 years of age head size is enlarged significantly, often to the point of macrocrania [Piven, *et al.* 1995, 1996; Davidovitch, *et al.* 1996; Lainhart, *et al.* 1997; Bailey, *et al.* 1998; Fombonne, *et al.* 1999]. The higher than normal incidence rate of macrocrania continues in adults, but is much less pronounced and less common [Piven, *et al.* 1995, 1996; Bailey, *et al.* 1998; Kemper & Bauman 1998]. (*Some studies also report autistic children as tending to have abnormally small head sizes at birth, which may give clues to potential pathogenic triggers of autism, which won't be discussed here.*) A lack of evidence for hydrocephalus or similar diseases that ought to increase head size and a small number of post-mortem autopsies of autistic brains suggest that the increased head size is concordant with an increase in brain size, at least prior to adulthood [Piven, *et al.* 1995, 1996; Bailey, *et al.* 1998; Kemper & Bauman 1998, 1999; Courchesne, *et al.* 2001; Aylward, *et al.* 2002; Sparks, *et al.* 2002;

Bigler, *et al.* 2003; Lainhart 2003; Herbert, *et al.* 2003, 2004]. Contemporary imaging technologies (PET, MRI, and especially diffusion tensor MRI) have confirmed both the increased incidence of macrocrania and mean head size in young (pre-adolescent) autistics as well as a concordant increases in brain size (presumably concordant on an individual as well as group level) [Cody, *et al.* 2001; Courchesne, *et al.* 2001, 2003; Aylward, *et al.* 2002; Brambilla, *et al.* 2003; Herbert, *et al.* 2003, 2004; Lainhart 2003; Barnea-Goraly, *et al.* 2004].

The results of the most recent studies strongly suggest that the *rate* of head and brain growth in autism is greatly increased in the first 2-3 years of life followed by normal or slightly increased growth after that until adolescence, when growth either plateaus or regresses slightly [Courchesne, *et al.* 2001, 2003; Aylward, *et al.* 2002; Brambilla, *et al.* 2003; Herbert, *et al.* 2003; Lainhart 2003]. The above studies, Courchesne, *et al.* (2004) in particular, describe what could be referred to as early onset adulthood with regard to size or simply as increased brain maturation rate; the above studies that closely examined brain and brain-subregion growth did not include adult comparisons, but the volume regression seen in adolescent autistics seems qualitatively similar to that seen in adults after the burst of synaptogenesis and white matter expansion that occurs during adolescence in normal individuals [Luna & Sweeney 2001].

The increases in brain maturation rate were not uniform, however. A great many studies have been devoted to investigations of size anomalies in autistic patients; however they have tended to suffer from small samples sizes and a insensitivity to the possible importance of patient age as a variable in the expression of developmental disorders making their results somewhat difficult to refer to as a whole. Herbert, *et al.* (2004), for instance attempts to draw conclusions about the sub-regional differences in autistic development through examination of a single age group. Many of the above studies *do* examine sub-regional differences in maturation rate. Aylward, *et al.* (2002), supported by other studies, found that while all brain areas increased in young autistics on an absolute scale, *as a fraction of brain volume* subcortical gray matter actually decreased and cortical gray matter remained relatively constant compared to normal controls. The greatest

difference between controls and autistics (in terms of fractions of total brain volume) was found in the increase in cortical white matter in autistic brains. That may not be surprising given that the first 2-3 years of life are a point of major synaptic pruning and glial proliferation, the latter accounting for most of the volume of white matter proliferation during the same period [Yakovlev & Lecours 1967; Brody, *et al.* 1987; Kinney, *et al.* 1988]. A number of studies confirm that white matter proliferation appears to be the most conspicuous change in early autistic brain development, though some of the particulars vary from Aylward, *et al.*'s (2002) study [Courchesne, *et al.* 2001, 2003; Aylward, *et al.* 2002; Brambilla, *et al.* 2003; Herbert, *et al.* 2003, 2004; Barnea-Goraly, *et al.* 2004]. In particular, Courchesne, *et al.* (2001) found significant, in fact concentrated, increase in white matter in the cerebellum (approximately twice the net abnormal increase of the whole brain white matter fraction) and Herbert, *et al.* (2004) found that the white matter increases appeared to be localized to the lateral regions of the brain in 9 year old autistics.

It is difficult to analyze differences in results between the different studies at this time due to their novelty and the differences in methodology. For instance, Courchesne, *et al.*'s (2001) paper sub-divided white matter fractions during their analyses, specifically analyzing cerebellar white matter, while Aylward, *et al.* (2002), as they noted in their paper, did not and so cerebellar increases in white matter may have been clouded by flatlined or even negative changes in some subcortical regions. Another possibility (also mentioned in the last two papers) is that, in addition to relatively small sample sizes, differences in the age groupings used for analyses as well as consistent intra-age group variability may have obscured some results. The absolute and relative volumes of different sub-regions and the brain as a whole have been shown to vary, not directly in all cases, and it is entirely possible that the relationship between brain sub-regions change over the course of development so that choosing certain age groups might exaggerate anatomical changes while obscuring others that are divergent around a particular point in development. It is clear that that is the case in many instances [Kinney 1988; Lunna & Sweeney 2001]. Because the relationship between time and differential regional maturation is not always (if ever) symmetrical about a particular time intra-age-group

variability can conceivably skew results significantly especially when compared to controls that may have a similar average age but a different intra-group distribution of ages.

That critique applies especially to the Herbert, *et al.* (2004) study. Despite being the most detailed sub-regional white matter analysis to date, and also uses a very tight age grouping (9 years of age, rather than 9-12 years of age or similarly wide groupings) the study examines only one age group. Because we may (and appear to) be looking at *maturational* acceleration rather than acceleration of *growth* (maturation sometimes entailing regression as well as growth) and because we have reason to believe that the rate of growth acceleration is constant in the first place, the very small window that Herbert, *et al.* (2004) provide us into autistic brain development, detailed though it may be, is insufficient to extrapolate rules governing the course of development across significant lengths of time. Additionally, while likely a minor concern, maturational changes, or maturational time if you will, isn't necessarily the same thing as 'absolute' time. The onset of puberty, for instance, while grossly consistent, varies significantly among individuals. It may be better to track developmental changes, such as voice deepening and appearance of facial hair, relative to each other than relative to earthly orbits around the sun. Future and current longitudinal studies of brain development also might want to chart developmental progression along a 'normalized' time line, based on the onset of other developmental changes rather than progression of absolute time. Doing so may decrease inter-subject variability and facilitate discovery of consistent differences among individuals that might otherwise be 'averaged out' by treating maturation as a simple function of the progression of absolute time.

Regardless, taken together, studies on brain, particularly white matter, maturation in autistic persons strongly suggest asynchronous acceleration of development in autistic individuals. Whether that asynchronous developmental acceleration is a cause or effect of a common underlying pathology is unknown, but does provide a new avenue of investigation into autistic etiology.

I can think of no *a priori* reason to assume that because white matter proliferation demonstrates the greatest enlargement that it is some who more *fundamental* to autistic etiology or pathology, however, because its function is nominally simpler than that of gray matter (ostensively transmitting data rather than "processing" it) characterizing deficits arising from its abnormality may be somewhat simpler as well. While white matter is a complex tissue, distinct from gray matter in a number of ways, the most conspicuous of those is in the existence of myelinated axons and the "long-range" connections established via white matter tracts [Baumann & Pham-Dinh 2001]. The gross connections appear to have been established early in development, which as has been suggested by multiple authors cited above, implies that increased myelination (of axons) is responsible for the increase in relative white matter volume. An increase in myelination ought to decrease signal lag across multiple spatial scales resulting in a number of effects that may be salient to functional and architectural development and may help explain autistic deficits.

3.6 Signal Delays & Synchronization in Neural Networks

Multiple factors contribute to conduction speed along an axon, including the stimulation history and geometry of the axon, but in the majority of cases, especially for long axons, myelination and axon width are the primary sources of variation in conduction speed, with a 100 fold difference in conduction speed between many small unmyelinated and large myelinated axons [Baumann & Pham-Dinh 2001; Debanne 2004]. Myelination is regularly assumed to increase the 'efficiency' (temporal and metabolic) of signal transmission and facilitate communication between disparate neural areas, however, the specific contribution that changes in signal delay (as a result of conduction speed *or* transmission distance) can make are rarely discussed in detail.

Given that neurons can produce action potentials or EPSPs with high levels of temporal precision [Mainen & Sejnowski 1995], that temporal correlation of firing patterns can be maintained through multiple stages of a neural circuit [Kimpo, *et al.* 2003], and that synchronization of inputs relative to the membrane time constant of neurons is fundamental the computations they perform[Hebb 1949; Debanne 2004] the significance

of signal delay on neural functioning, and particularly neural development is potentially great. Synchronization of inputs is fundamental to the cell assembly hypothesis, which roughly states that the synchronized firing of neurons indicates co-processing of external and internal stimuli and may be a basic diagnostic for functional organization in neural networks [Hebb 1949; Freiwald, *et al.* 2001; Engel, *et al.* 2001; Rolls, *et al.* 2003]. While 'rate codes' are considered to be an important part of neuronal communication the *timing* of firing across individual neurons is fundamental even to the generation of rate codes, can carry significant information by itself,[Abeles 1991; Murthy and Fetz 1996; Riehle, *et al.* 1997; Dan, *et al.* 1998] and may be even more effective at driving "downstream" neurons [Usrey, *et al.* 2000]. Increased myelination, and thus decreased signal delay, ought to increase synchronization of neural firing, especially between disparate neurons essentially facilitating communication between nodes; both by better maintaining the integrity of temporal rate codes and facilitation of the co-firing of disparate neurons within given epochs (allowing functional cellular assemblies to be constructed from larger neural networks) [Carr & Konishi 1988, 1990; McAlpine & Grothe 2003].

Myelination, as typically occurs during white matter proliferation, can be thought of as a means of increasing the neural resource allotment at a given time. Advanced white matter proliferation, as observed in autism, may take on the character of advanced resource allocation during development adversely affecting developmental synchrony. It is worth noting that neural maturation may be activity dependant, in which case white matter proliferation could both cause other forms of neural maturation and be caused by it [Barres, *et al.* 1994; Quartz & Sejnowski 1997; Stevens, *et al.* 1998; Pombo, *et al.* 1999; Turnley & Bartlett 1999; Jensen, *et al.* 2000; Stevens & Fields 2000; Levine & Black 2001; Fields & Stevens-Graham 2002; Kühl, *et al.* 2002]. This paper will not attempt to examine that issue in detail due to the ultimate similarity of a variety of different possible means of neural maturation in the developing brain, but will simply leave open the possibility that some form of advanced neural maturation is taking place. The fact that the neural maturational abnormalities in autism may ultimately affect the allotment of neural resources will be a focus.

3.7 Increased Neural Density

Increased neural density (increased neural number and decreased neural size) has been consistently reported in autistic brains [Bauman & Kempler 1994; Kemper & Bauman 1998; Casanova, *et al.* 2002]. Increased neural density has even been suggested to be fundamental to the etiology of autism as a result of an over-abundance of resource argument similar to the one presented here in some ways. Increased neural density may very well contribute to autistic cognitive and neurological abnormalities; however it may also be a side-effect of advanced neural maturation, including white matter proliferation. Astranomical numbers of neurons die of in the first years of life and it appears that neuron survival is dependant at least in part on chemical factors releases as a result of synchronized firing between neurons and their efferents [Purves 1986]. If this is the case then increases in synchronized neural firing ought to result in a greater percentage of surviving neurons if the activity dependant survival is measured on at least a pseudo-absolute scale (i.e. if it synchronized activity levels are 'measured' relative to nearby neurons then the percentage of surviving neurons would very likely not change) [Miller, *et al.* 1989; Jacobs & Jordan 1992; Miller 1995]. If that *is* a mechanism accounting for the increased neural density in autistic brains then the degree to which density, or at least number, is increased should be at least partly proportional to how much earli*er* advanced white matter proliferation affects areas relative when major neural culling occurs ("partly" because other brain abnormalities might also affect activity levels and neuronal survival, especially later in development). While it is not clear exactly how and when culling occurs in different areas of the brain, it is relatively uniform, occurring slightly earlier in earlier developing areas of the brain.

That meshes well with observations of autistic brains that show increases neural density primarily located in areas that myelinate early, but not earliest, in normal development. If advanced myelination were at least partially responsible then we would expect little difference in the earliest myelinated areas, because they would have been myelinated early enough in normal humans to already benefit from increases synchronicity, and less in late developing areas, because neural culling would have already

occurred there [Yakovlev and Lecours 1967; Brody, *et al.* 1987; Kinney, *et al.* 1988; Shrager & Johnson 1996]. The lack of precise neural maturational maps makes interpretation difficult, but strongly support a role for advanced neural maturation in the genesis of increased neural number in autistic brains. The reason for decreased neural size in some cases is not clear, and may not occur in all cases where increased number does occur (as already noted, some brain areas demonstrate normal levels of density and increased size). Decreased neural size might be a result of crowding or diminished arborization due to learning abnormalities resulting in fewer connections and thus lower soma size due to decreased metabolic demands, but could certainly be a result of a number of other factors. It is even possible that increased synchrony resulting from said mechanism results "washes" out differences in activity synchronization between neurons, resulting in a more equitable distribution of neurotrophic factors and thus smaller size and decreased morbidity—ignorance regarding the details of the relevant cellular dynamics obscures responsible mechanisms.

3.8 Delocalization of Functional Neural Modules

Functional localization in the normal human brain appears to be very common for concrete and abstract representations, but appears greatly decreased in the autistic brain [Schultz, *et al.* 2000; Allen & Courchesne 2001, 2003; Pierce, *et al.* 2001]. Functional delocalization in autistics subjects ties in exceptionally well with theories of advanced neural maturation, particularly theories of advanced myelination. Two lines of reasoning (that ultimately prove to be essentially the same) strongly point to a relationship between white matter proliferation and functional localization of neural modules. The first is simply the extension of the model of white matter as a facilitator of long-range neural communication. If that is the case then advanced white matter proliferation ought to have the effect of increasing long-range neural communication within the brain, which in turn should result in an increase in the neural area exposed to stimuli at any one point in development and a wider area dedicated to processing incident information. If we assume that at least some changes in the types of processing done in different areas is a result of previous learning and not just neural resources available then increasing the resource

allotment at a given point ought to result in wider distribution of neurons executing certain functions. Cell assembly theory is predicated on the idea that cells that fire together within a certain time frame more than would be predicted by the coherence of incoming information (relative to those neurons) represent functional assemblies of neurons that are co-processing same or similar data [Mainen & Sejnowski 1995]. An increase in the number of cells that then are able to synchronize their firing ought to increase the possibility of cells that *can* co-process data very likely resulting in functional delocalization.

The second comes from studies of time varying neural plasticity. The so-called "wave of plasticity" model suggests that a "wave" of plasticity that migrates at an appropriate speed across a neural network over the course of development will result in different portions of the network being most susceptible to change at particular times [Jacobs & Jordan 1992; Shrager & Johnson 1996; Jacobs 1999]. Because not all functions are learned simultaneously by the network (an effect heightened by the effective progressive increase in neural resources—since areas that do not become plastic until later are effectively non-functional in earlier learning), varying local plasticity with time can result in functional localization. Localization is severely decreased if the 'plasticity wave' migrates too quickly, and to a lesser extent if it migrates to slowly, because the spatial plasticity changes and functional learning become desynchronized (the case is much less severe if the wave migrates too slowly because the available resources are so much reduced that further learning is hampered until additional neural resources become available) [Jacobs & Jordan 1992; Jacobs 1999]. It has already been established that increases in neuronal synchrony resulting from decreased signal delay have the same effect as increases in neural plasticity so long as newly "connected" areas are functionally undeveloped—as is likely the case, for the most part, in the developing human brain. Current artificial neural network models also assume that as the absolute value of interneuronal strengths increase plasticity decreases, implementing the decreasing side of the 'wave of plasticity model' (with the added advantage of having synchronized the decrease in plasticity with learning on an individual neural level) and appears to be biologically realistic [Elman 1993; Turrigiano 1999]. Theories of learning dependant on synaptic pruning, Hebbian learning, or neurotrophic agents tend to posit a degree of

sigmoidal plasticity relative to the absolute value of synaptic strength [Cowan, *et al.* 1984; Purves 1986; Geman, *et al.* 1992; Elliot & Shadbolt 1998]. The arguments pertaining the 'wave of plasticity' model should apply to a 'wave of synchronicity' model as well—which progressive localized white matter proliferation and myelination (as well as other aspects neuronal maturation) likely effect. Certainly not all neural activity demonstrates delocalization in autistic persons though. Relatively later developing functions in particular, such as attentional networks within the cerebellum,[Allen & Courchesne 2001] higher-order 'binding' in visual cortex,[Grice, *et al.* 2001] and "executive" network activity in the prefrontal cortex [Miller 2000; Miller, *et al.* 2002] often seem to display lower overall activity levels and seem to recruit less neural area. Unfortunately on systematic studies have sought to compare localization and delocalization of neural modules in autistics subjects or between knowledge humans in general for a variety of modalities/modules. It appears that most of the modules or tests not demonstrating delocalization tend to be of functions that autistic are either not very good at, develop later than other functions in nearby areas of the brain, or often both—though this is not uniformly the case, "face perception", for instance, is considered to be a weak ability in autistics, yet demonstrates substantive delocalization. It is possible that some functions that autistics are particularly weak on simply generate less activity, making statistical discrimination of differential task activity difficult to discern. Another, non-exclusive, possibility, which is discussed in the following section, is that the delocalization of functional modules "crowds" out later developing modules, resulting in extremes of localization and delocalization. Further research is obviously warranted.

3.9 Crowding

Increasing the neural resources allotted to developmentally earlier tasks *might* not cause significant problems or even be advantageous if neural resources were not ultimately limited, but, even if with possible advantages of increased neural density or number, autistics are still faces with a resource ceiling that may seriously hamper their cognitive & neural development. In particular, the phenomenon of delocalization of functional neural modules in autistics begs the question of whether there is greater inter-leaving of

functional domains in autistics subjects and if so to what extent or a greater number of neural resources are dedicated to certain functions. Ambiguity about the nature of neural processing and shortcomings, theoretical and 'material', of neural imaging methods preclude a definitive answer to that question—even in principle. However, a significant amount of evidence implies functional "crowding" in autistic brains, with relatively early developing functions and sometimes even neural areas, apparently taking up greater amounts of space than later developing ones—the implication is that later developing functions/areas "ran out of room" to develop due to excessive neural resources ("space") occupied by earlier developing functions. This could explain a number of phenomena involving abnormal function of later developing modules such as the much larger amount of neural area devoted to simpler motoric functions in autistic cerebella relative to that dedicated to attentional functions,[Allen & Courchesne 2003] and in particular the executive dysfunction thought to underlie many autistic traits (with executive deficits being among the last to develop)[Miller 2000; Blair, *et al.* 2002; McAlonan, *et al.* 2002; Schmitz, *et al.* 2003; Tecchio 2003].

"Crowding" was originally used in the context of persons with brain damage to areas such as the left-hemisphere that nonetheless developed normal function with regard to modalities (such as speech) normally thought to be confined to the damaged areas, but who demonstrated deficits in other modalities instead [Teuber 1974]. It was suggested that the 'more important' functions took root where they could, but ultimately "crowded" out other functions as a result [Nass & Stiles 1996; Allen & Courchesne 2003]. It is difficult to argue what "more important" means on different levels of the nervous system, but it is certainly conceivable that earlier developing functions take up space that would otherwise be allotted to later developing ones, indeed, that may be another important reason why neural maturation must be so slow.

Multiple factors could theoretically cause such crowding, autistic traits such as "repetitiveness" and sometimes excessive attentional focus or insistence on consistent environments could possibly, for instance. That could result in an excessive enlargement of areas dedicated to simpler functions, causing crowding, or even result in simpler functions

becoming more connected with other areas of the brain creating the illusion of crowding in neural imaging experiments. The evidence and arguments discussed in this paper regarding advanced maturation and allotment of neural resources and in particular delocalization of functions suggest that crowding may be a result of hyper-maturational mechanisms and the phenomenon is certainly consistent with such theories.

3.10 Impaired Abstraction

One of the most striking "cognitive" deficits displayed by autistics is a difficulty grasping "abstract" concepts and an impaired ability generalize learned information [Gillberg & Coleman 1992; Baron-Cohen, *et al.* 2000; Schmitz, *et al.* 2003]. Some of this may be a result of the crowding of later developing functions discussed above, in particular functions subserved by the late developing prefrontal cortex (PFC), such as "abstract thought", complex decision planning, and working-memory could be impaired in autistics and could conceivably impair "abstract" thought and generalization [Miller 2000; Miller, *et al.* 2002]. However, most of the PFC does not mature or myelinate until after puberty in normal humans and appears correspondingly quiescent until around that time [Sowell, *et al.* 1999; Luna & Sweeney 2001]. As autistics display abstraction and generalization impairments realtive to their peers throughout childhood, before areas like the PFC have come "online" in normal children, indicating that the roots of said abnormalities have other origins as well.

Three very interesting models that could ultimately account for deficits like the one's just mentioned have been proposed: that that excessive neural density, highly conjunctive coding (biological mechanism unspecified), or excessive interneuronal inhibition might result in a certain inflexibility of processing [Cohen 1994; McClelland 2000]. Advanced neural resource allocation, such as by advanced white matter proliferation, could also provide an explanation to said abnormalities. One of the strong attractions of artificial neural networks (ANNs) is their ability to effectively generalize what they've learned from certain information sets to novel information sets in uncannily appropriate ways, even in very simple ANNS [Hare, *et al.* 1995; Baum & Haussler 1989].

The robustness of particular network representations depends on a number of factors however, of particular interest is that in multilayered networks the robustness of representations is especially dependent on the number of context-nodes (non- input or output nodes) used to represent a given item [Baum & Haussler 1989]. Too few nodes predictably results in impoverished representations that do not capture the complexity of the data set and result in relatively inappropriate output in certain cases for the training data and novel data. Once sufficient numbers of nodes are present to accurately represent the training data increasing that number will usually not adversely affect behavior from the same training data, however it usually *will* adversely affect the networks ability to make predictions based on *novel* data. There appears to be a 'sweet spot' where if just enough neurons are present the ANN will represent training data accurately and in a manner that highlights salient relationships, that makes default abstractions [Baum & Haussler 1989]. Fewer nodes and representations are too crude, more nodes and the network begins to operate like a statistical "look up table" no longer coding salient abstractions. Why this is arguable, it is likely because the representations that are most "salient" (appropriately abstract) are also the most efficient in most cases (depending on the actual abstraction in the data and what abstractions the human trainers prefer to focus on, of course) such that the smallest network size that can accurately represent the training data can only do so with such efficient abstractions.

Larger networks may be *capable* of such abstractions, but first wind up in a state that represents the *training* data equally well either through simple chance (the number of possible network states that accurately represent the data almost certainly increases with network size beyond the most efficient, with the most efficient just being no more likely than many inefficient others) or because inefficient "look-up" representations are actually easier to devise from the quasi-random starting points that most networks are set on. *[my network]* In autism, if the neural resource allotment is increased early in life then it is plausible that the excess of resources results in inefficient and thus less generalizable neural representations affording the peculiar abnormalities described.

3.11 Weak Central Coherence

A popular theorized autistic deficit called "Weak Central Coherence" (WCC) attempts to capture the impaired abilities of autistics to use conventional abstract concepts and a reported tendency to focus on "parts" rather than "wholes" and an inability to use "context" [Mottron, *et al.* 1999; Plaisted, *et al.* 1999; Grice, *et al.* 2001; Bertone, *et al.* 2003]. Unfortunately, as Cohen (2003) has noted, proponents of WCC offer few specifics regarding how central coherence is judged, and at what levels of processing central coherence is impaired; it would seem that "context" and "central" coherence are references (understandably) to whatever otherwise normal children seem to use in tasks where autistics perform abnormally. The tendency of abstract impairment or WCC to occur at a level corresponding to most levels that normal humans perform would be strange if the biological nature of the deficit were non-developmental, but as was described in the above section on impairment of abstraction in autism, abnormalities of normal developmental mechanisms could create such uncanny variety of deficits by affecting learning itself rather than simple 'output'. Advanced allotment of neural maturation, as by white matter proliferation, seems to provide an excellent starting point for the explanation of WCC-type deficits in autistics by directly affecting the levels at which learning and abstraction occurs. However, WCC also encompasses other proposed autistic deficits such as an impaired ability to use context in processing (even in the cases where "context" consists of items that can be processed individually) and also related to other deficits such as apparent hyperacuity in certain psychophysical tests such as tone discrimination,[Neville, *et al.* 1994; Bonnel, *et al.* 2003] superior performance on tests demanding detailed analysis of visual features or selective focus on component features (e.g. Weschler Intelligence scale Block Design subtest, "embedded figures test", or visual search tests),[Lockyer & Rutter 1970; Tymchuk, *et al.* 1977; Shah & Frith 1983; Joliffe & Baron-Cohen 1997; O'Riordan, *et al.* 2001]. Failure of autistics to adequately 'gate' sensory stimuli may be partly related to hypersensitivity as well [Neville, *et al.* 1994; Gepner & Mestre 2002] though executive dysfunction or other attentional abnormalities (perhaps involving the cerebellum) may also be responsible [Goldman-Rakic 1994; Courchesne, *et al.* 1994; Allen & Courchesne 2001]. Happé (1996) reported that autistic persons are also less susceptible to visual

illusions (perhaps because of reduced use of context), but that effects has not been consistently replicated [Ropar Mitchell 1999].

It may be that rather than just learning less efficiently autistic children also process very different information. In the case of the ANNs discussed earlier, even those with unnecessary nodes *did* manage to represent the training data very well, we might ask ourselves what the "training data" is in the case of a human child, autistic or otherwise. The "richness" of incoming environmental stimuli, different and less precise though it may be for children and infants, allow one to conceivably draw an incredible array of relatively veridical abstractions. The larger resource availability due to advanced neural maturation would allow representation of relationships that are difficult to abstract efficiently and the lower level of functional (and 'abstract') development would mean that there would be less basis for interpretation of data on abstract levels and less modulation of attention at such levels. Early, and relatively crude relationships, like tone or hue discrimination might be enhanced in autistic brains as could more 'advanced' concepts, but devising the necessary tests could prove difficult. The, already mentioned, inefficient neural representations and advanced level of representation of some functions might also affect the ability of autistics to process the numerous items that constitute "context" (especially if they are processed more abstractly as parts of "context") due to the limitations on working memory or other neural mechanisms. If that is the case then in those cases it is reasonable to expect that acontextual processing would increase with age (relative to age-matched peers) because of the greater neural resources available early in life (again, relative to age-matched peers). The additional neural resources available might have also allowed autistic brains to capture certain relationships without resorting to contextual cues that normal brains would have had to—in that case neural representations might be learned in such a way that they are essentially a contextual; which shouldn't result in the same exacerbation of acontextual processing with age, perhaps even the opposite as neural representations change over time and take into account new information.

3.12 Islets of Ability

Probably related to WCC-type abnormalities the rate of autistics demonstrating savant-like abilities, abnormally high cognitive function covering a narrow islet of abilities, is much higher in than in normal or most other cognitively impaired groups [Tymchuk, *et al.* 1977; Mottron & Bellville 1993; Goldman-Rakic 1994; Neville, *et al.* 1994; Frith 1997; Snyder & Mitchell 1999]. Some savant-like skills may be a result of forming abstractions between information that would otherwise remain un-unified in normal brains, for instance some autistic savants are able to calculate any day of the week for any day of the year for hundreds of years forward or backwards [Snyder & Mitchell 1999]. There happens to be very nice mathematical formulae that allow one to do this, but they are not ones that people tend to spontaneously realize as do some autistic savants appear to do. Similarly, extraordinary memory abilities of savants, the ability to memorize entire phonebooks for example, may be more than a result of 'extra-time on their hands' that allows them to practice or even just a result of additional neural resources dedicated to simpler tasks, especially salient representations of certain basic information might actually make some autistics savants more efficient at such seemingly rote tasks.

One resulting question is whether autistics might actually learn more quickly (and accurately) within narrow contexts. While it is relatively clear that present learning occurs at least in part in the context of past learning, and indeed early inability to make coherent sense of their environment may critically stunt autistic cognitive growth, however it is possible that in many cases relatively normal cognitive growth is possible and more simply narrowed and channeled. For instance, anecdotal evidence suggests that despite critical social inability in many contexts autistic children may actually be much more receptive and aware of emotionally revealing cues on the part of their mother or other close caregiver [Dawson, *et al.* 2002]—which would be consistent with the autistic brain having created an accurate representation of the "training data" their mother, even precociously so, (whom they gained great deal of exposure to, and whose behavior they also probably have a particular emotional interest in) but are unable to generalize what they've learned.

3.13 Critical Windows

Extending the idea of collapsed developmental time some autistic deficits can be construed as failures to gain sufficient and appropriate exposure within collapsed "critical windows" of development. Severely impaired linguistic faculties of autistics could be an example of this. Critical windows are not well understood themselves, and are certainly not the ultra-rigid all/or none timer periods that they have often been construed to be, at least not in all cases [Bourgeois, *et al.* 2000; Kuhl 2000; Neville & Bavelier 2000]. Some critical windows may also be mediated by the separate developmental mechanisms becoming incidentally coincident—Turkewitz & Kenney's (1982) theory of visual size constancy would be an excellent example. The ability to learn size constancy was dependant on the coincidence of separate mechanisms mediating visual depth of field and more complex visual learning—mechanisms whose development does not appear to be explicitly synchronized. Using the concept of "developmental time", we can think of the last example as illustrating separate time continuums. Separate developmental trajectories, or continuums, during development for separate substrates introduce another opportunity for developmental dysynchrony and beg the question of what developmental trajectories may fail to synchronize in the case of advanced neural maturation. One area of development that is may not be as significantly affected by advanced neural maturation in the CNS is low level visual ability.

Spatial frequency, visual acuity, and contrast sensitivity in human vision gradually matures from being constrained to very low to including much higher levels of spatial frequency over the course of the early development [de Schonen & Mathivet 1990; Simion, *et al.* 1998; Teller 2001; Mondloch, *et al.* 2002]. The mechanisms responsible for such development are largely unknown, but appear to be localized to very early levels of V1 cortex or its afferents (e.g. the LGN), areas whose gross neural maturation, and certainly, myelination occurs early enough in normal development that advanced neural maturation may have much less effect [Teller 2001]. One result of this may be that higher-level visual areas that would normally be trained on relatively detailed, high-frequency visual information are instead trained on much cruder stuff, crowding out some later developing

functions in the manner discussed before. This would not be particularly notable except that it may provide a functional analogy to the visual development of persons with congenital cataracts. Cataracts severely impair vision, and almost always eliminate detailed vision, depriving developing visual areas of the stimuli they would otherwise have had if the cataracts are not removed early enough, sometimes causing various visual deficits if the cataracts are not removed by certain points in the children's' development. The advanced gross neural development in autistics may result in earlier 'receptivity' and learning of visual areas, creating a deprivation not unlike that in persons with congenital cataracts because of the failure of spatial frequency to advance at an equivalent rate.

Strikingly, both autistics and persons with left-side cataracts not removed prior to about 6 months of life display markedly similar face perception deficits and even some neural activity abnormalities for the rest of their lives (the left eye, presumably, because facial processing is uniquely dependent on activity localized to the right fusiform gyrus) [Le Grand, *et al.* 2001]. Among those abnormalities is the putative failure to use 2^nd^ary features or "configural processing" to aid in facial identification, evidenced by decreased ability to use facial context in order to process recognize 'parts', significant inversion insensitivity (a relative insensitivity to certain manipulations that have a marked effect on normal adult viewers), and generally poor face recognition and memory abilities [Schultz, *et al.* 2000; Adolphs, *et al.* 2001; Grelotti, *et al.* 2002; Teunisse & Gelder 2003]. Deficits in face perception resulting from congenital cataracts are thought to arise due to deprivation during a critical period of development (which is theorized as resulting from coincident myelination of the right fusiform gyrus and onset greater availability of spatial frequency, visual acuity, and contrast sensitivity, is "missed"—an excellent parallel of the theory of advanced neural maturation, particularly advanced white matter proliferation, in autism). Both persons whose congenital cataracts were not removed within the appropriate period and went on to develop face processing deficits and autistics with face processing deficits also fail to display characteristic activity in the right fusiform gyrus region and other regions associated with face processing, implying that the normal neural substrates that underlie such processes either failed to take them on perform properly. Differences in neural activity certainly exist between the two groups even in areas such as the right

fusiform gyrus (in particular, autistics' tend to display a less localized neural activity),[Schultz, *et al.* 2000; Adolphs, *et al.* 2001; Grelotti, *et al.* 2002; Teunisse & Gelder 2003] but this is not surprising given the pervasive nature of autistic disorder and the discussed effects the model proposed in this paper may have on neural development.

3.14 Impaired Social Ability

Impaired social ability, particularly social interest and extra-personal insight, have traditionally been the defining symptoms of autism [Rapin 1994; Reed 1994; Sigman 1994; Dawson, *et al.* 2002; Russell, *et al.* 2003]. (The disorder was actually named for those deficits, "autistic" originally being a term used to describe totally self-conceited beings, such as infants according to the opinion of Freud.) "Theory of Mind" deficits have been posited, suggesting that some quasi-coherent system dedicated to representing other people's minds has gone awry in autistics [Happé 1999; Dawson, *et al.* 2002; Abu-Akel 2003; Gallagher & Frith 2003]. With proponents pointing to autistics' failure on "false belief" tasks (e.g. someone sticks a doll under bucket A while Sally is watching, then moves it to bucket B while she isn't watching—you ask the child which bucket Sally will look under for the doll. Even though the child knows that the doll is under bucket B, an appreciation of the limitations of Sally's knowledge ought to render the decision bucket A. Autistic children are notoriously poor at these types of tasks) [Frith & Frith 1999]. Less striking theories have suggested that emotional perception (and perhaps experience) are impaired, citing evidence of amygdalar dysfunction and its importance both to emotional processing and evidently emotional perception [Adolphs 2002; Daenen, *et al.* 2002; Arana, *et al.* 2003; Bauman, *et al.* 2004]. Suggestions that communication and emotional awareness deficits stem from indirect sources, such as impaired face perception obfuscating the social realm and making social learning difficult, have also been made [Adolphs, *et al.* 2001; Grelotti, *et al.* 2002]. Neural network models involving excessive interneuronal synaptic inhibition and attentional models have proposed to account for at least some autistic deficits (in particular failure in false belief tasks) [Roth & Leslie 1998; Leslie 2000].

The paucity of knowledge regarding the functionally diverse "class" off skills and abilities involved in social interaction makes it exceedingly difficult to currently address 'social deficits' from a biological standpoint. Advanced neural maturation ought to have wide-ranging affects across most neural structures and functional modalities in autism due to its very early onset and there is no reason to believe that it might not account for social deficits, and most likely does in a number of ways. Proposed difficulties in assigning identities to individuals due to deficits of face "perception", impaired language acquisition, difficulty dealing with abstract concepts and generalizing new information, and possible 'awareness' of data relationships not noticed by normal persons have all been tentatively explained in terms of advanced neural maturation and would almost certainly affect social deficit. Effective social communication is dependent on some level of understanding of the other persons' goals, which are necessarily "abstract" [McCabe, *et al.* 2000; Boroditsky & Ramscar 2002]. Significant, even minor, differences in cognitive concept may severely derail normal social interaction, not because autistic persons are not interested in social interaction but because persons in autistic-other interactions do not appear to operate in a subjectively coherent manner to their opposite. Difficulty in establishing even non-linguistic or "non-formal" communication further might impede establishment of reciprocal interactions that would allow normalization of goals and concepts. (i.e. up to a point different cognitive contexts might be ultimately negligible, because communication can bring differing minds toward effective similarity, after a certain point that communication cannot be set up creating what appears to be a distinct divide between predisposition to sociality along a continuum of difference).

The boredom and even resentment evoked by interaction with subjectively incoherent systems appears to be common in humans [anecdotal observations]. That is, for instance, one of the main difficulties in scientific education—people show no interest in what dynamics that too them seem "random" or at best "arcane" (when they, usually on faith, accept that seemingly random dynamics have some order to them). If autistics persons, especially "severely" autistic persons, really have abstracted relationships in the world very different from normal those of normal persons, then it would be difficult to expect them to understand the normal persons' behavior, which is predicated on those

very relationships. This is supported by observations that when autistics do engage in social play it is usually abnormal, and doesn't involve normal social dynamics, (The DSM III listed the use (by the autistic person) of the other person as a "mechanical aid" for instance) autistics children apparently often become excited and interested if another person apes them for instance [DSM III]. Possibly, because the other person's dynamics are now conforming to rules that the autistic can understand, they are relatively simple and do not require alien referential abstractions (like cowboys and Indians). That many of the abstractions and relationships that humans utilize are learned at least in part by proxy, via social interaction, ought to exacerbate early 'social deficits'—requiring that the individual instead create/discover their own 'functional' relationships, which, unable to piggy back on past human achievements (because of lack of (effective) social interaction), are probably going to be much less abstract, than the ones we work with. Not unakin to the differences between an educated and aboriginal scientist, creating illusions of inherent difference when most of the differences in persons actually stems from different experience-histories.

3.15 Variable Individual Prognosis

Today autism is often considered a 'spectrum class' disorder, part of a larger class of "Autism Spectrum Disorders" (ASD) to which other disorders such as Asperger's syndrome, high- and low- functioning autism, pervasive developmental disorder, and delayed language disorder belong [Gilllberg & Coleman 1992; Waterhouse 1994]. The diversity of symptoms of the ASD disorders and the lack of a simple genetic correlate of the disorders has caused many researchers to assume that ASD is not an etiologically coherent set of disorders at all [Gillberg & Coleman 1992; Piven & Folstein 1994]. While to some degree that must be true, etiology must differ at least somewhat if the end result differs, and "initial" pathogenic causes may differ as well, but the similarity of core symptoms does suggest that common etiological mechanisms may be operating in all of the disorders, mechanisms that do not create a clear scale of pathological severity.

Advanced neural maturation would provide a mechanism that could theoretically account for the observed variety of disorders. Because the abnormalities stemming from

advanced neural maturation of the sort described in this paper are a function of the disjoint in synchrony between normal experience and gross neural development differences in individual experience can affect the outcome of the disorder. In particular, the advanced neural maturation may be thought of, on a crude level, as "compressing" developmental time relative to absolute or "experiential" time. The result, among many other things already discussed, is that the actual set of data on which learning occurs is drastically reduced. The effective decrease in "sample size" increases the importance of individual outliers and "noise", things that might otherwise be 'drowned out' over the course of development represents a much larger percentage of the autistic person's experience. The variability of autistic persons' experiences would also be drastically increased then due to this increased sensitivity to incoherence in their environment. A result might be that small differences in childhood environment, even and especially in infancy, might translate into gross effects on later cognitive development.

The difference between a person with Asperger's syndrome and high-functioning autism is clinically whether or not there was a delay in the onset of language (negative in the former and positive in the latter) [Baron Cohen 2000]. Rather than the two persons having differently susceptible 'language genes' or some other specific difference, it might be that the person with Asperger's was exposed to a somehow more consistent set of language-meaning relationships early in life than the high-functioning autistic. The effect could be small, relating perhaps even to the consistency of facial or gestural langue early in life, creating a bridge across which language could be learned, or perhaps the Asperger's person's parents spoke in smaller sentences or with particular kinds of grammar, perhaps they just spoke slowly. Lacking the developmental robustness of normal children ASD persons might be susceptible to a whole range of variables that are unrecognized because they are important only to this particular subset of persons. That is not to try to put "blame" on parents, though I have neither interest in doing nor not doing so, it is simply to suggest that the sensitivity of ASD persons might be different enough that very different considerations may need to be taken into consideration in order to unravel their distinctions. That also suggests that non-medical intervention may significantly help ASD persons. If part of what separates a high- from a low- functioning autistic is the consistency

of certain relationship that they are exposed to early in life then perhaps, especially with early diagnosis, ideal environments can be ensured through clinical intervention and caregiver attention.

3.16 Conclusions

It appears that most autistic abnormalities can be explainable by mechanisms of advanced neural maturation. The fact that the proposed model appears to successfully addresses behavioral, psychophysical, "cognitive", and neurological characteristics of autism and other ASD disorders necessitates serious consideration be given to the approach. While the models as described here may not accurately account for actual mechanisms responsible for autistic abnormalities, their theoretical success implies that they may point towards superior models in the future. Despite autism and ASD being labeled as "developmental" disorders, relatively little focus has been placed on how disorder during *development* may mediate the underlying etiology. A great deal of focus has been placed on genetic studies attempting to find the genetic "cause" of autism [Gillberg & Coleman 1992; Piven & Folstein 1994; Dawson, *et al.* 2002]. While a number of studies have strongly implicated heritable factors in autism this does not mean that the heritable genetic abnormality is the most salient link in the etiological chain [Gillberg & Coleman 1992; Piven & Folstein 1994; Bailey, *et al.* 1995; Dawson, *et al.* 2002]. As has been suggested in this paper, a number of different mechanisms of neural development may effectively substitute for one another in many cases, resulting in highly similar effects on behavioral and neural development despite different particulars. Similarly, ASD disorders may share a common etiology triggered by diverse pathogenic causes. The success of associating numerous human disorders with relatively specific abnormalities of the genetic sequence should not prejudice us to assume that all disorders have such simple relationships with genetic code. At the very least, scientific and clinical interests may often be better served by looking at post-cause etiology rather than excessive searching for pathogenic triggers themselves. The surgeon, faced with a wounded patient on her table, will be better equipped to save the patient's life if armed with knowledge about the effects of blood loss and shock, than the physics of skin rupture by bullets ... or knifes, or steel pipes, or any number of other objects/incidents that could cause the same essential

physical disorder in the patient. Regardless, further research, theoretical and experimental is clearly required in order to better assess the legitimacy of advanced neural maturation models ability to account for autistic abnormalities, or those of other developmental disorders.

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