We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 3

The Role of Cortical Modularity in Tactile Information Processing: An Approach to Measuring Information Processing Deficits in Autism

Eric Francisco, Oleg Favorov and Mark Tommerdahl

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54801

1. Introduction

Autism is a pervasive developmental disorder that is manifested in a number of neurological alterations. Although there is a large spectrum of behavioral excesses that includes a diverse number of traits, such as repetitive behaviors and/or sensory hyper-responsiveness, many of the neurological problems could be attributed to underlying anatomical and physiological fundamentals that demonstrate significant diversity within this spectrum and make the phenotypic description of the disorder distinctly different from that exhibited by normal physiology. Characterization of neurological features – such as cortical modularity – could lead to a better understanding of the neurophysiological fundamentals of autism. Recently, we have been developing sensory-based diagnostic protocols based on neurophysiological principles that have been elucidated in animal studies conducted both in our laboratories and those of others. One question that we have pursued in our animal studies has been the fundamental role(s) of the cortical minicolumn and macrocolumn in tactile information processing. We have developed experimental models for determining cortical correlates of perception that relate cortical activity patterns in somatosensory cortex (at high resolution in squirrel monkey studies) to measures of human perception. The minicolumnar and macrocolumnar organization of the cerebral cortex is dynamic and interactive, and the patterns of activity that are generated with stimulus-driven activity in SI cortex have been shown to be modular in nature. This determination of modularity is derived from a self-organizing process that takes place via dynamic interactions between minicolumns and columns in the cortex both during and after development. If developmental processes malfunction, then cortical organization suffers at a number of scales. Findings by Casanova and colleagues have elegantly demonstrated in post-mortem histological experiments that minicolumn organization in

INTECH
open science | open minds

© 2013 Francisco et al.; licensee InTech. This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

autism is severely compromised, as there are approximately 30% more minicolumns in the same cortical space as is normally found [1]. The increase in minicolumn density, and particularly the decrease in neuropil between the minicolumns (because they are now much more densely packed), led us to make a number of predictions about alterations in perceptual metrics that would occur in individuals with autism. In this paper, the neurophysiological basis of three such perceptual metrics (previously reported) is discussed.

2. Cortical modularity and spatial localization

In 1978 Mountcastle [2] hypothesized that the smallest functional unit of neocortical organization, the "minicolumn", is a radial cord of cells about 30-50μm in diameter, and that sensory stimuli activate local groupings of minicolumns (called "macrocolumns"). This hypothesis subsequently received support from multiple lines of experimental evidence and led to its substantial elaboration. Structurally, minicolumns are attributable to the radially-oriented cords of neuronal cell bodies that are evident in Nissl-stained sections of the cerebral cortex and it is probable that they are related to ontogenetic columns [3] and to the radially-oriented modules defined by the clustering of the apical dendrites of pyramidal neurons [4]. Among the various elements of neocortical microarchitecture, *spiny-stellate* cells and *double-bouquet* cells [5-7] are most directly relevant to Mountcastle's concept of the minicolumn. Spiny-stellates are excitatory intrinsic cells that are especially prominent in layer 4 of primary sensory cortex. They are the major recipients of thalamocortical connections and, in turn, they distribute afferent input radially to cells in other layers. Double-bouquet cells are GABAergic cells whose somas and dendritic trees are confined to the superficial layers, and because the double-bouquet cells are more likely to inhibit cells in adjacent minicolumns rather than in their own, they offer a mechanism by which a minicolumn can inhibit its immediate neighbors.

Some insights into the role of the minicolumn in sensory information processing have been revealed through neurophysiological experimentation. Receptive field mapping studies by Favorov and colleagues [8] determined that there are abrupt shifts between receptive field centers as stimuli shift from one skin site to another. In other words, Favorov's receptive field work predicted that a perceptible but subtle shift of stimulus position would not necessarily engage a different pattern of macrocolumnar activity. Rather, the pattern of minicolumnar activity *within a macrocolumn* would be different with a shift in stimulus position up to a point. At the point at which the stimulus position crosses a boundary, the stimulus will engage a new macrocolumn and an entirely different minicolumnar pattern of response will be evoked by the stimulus. Figure 1 summarizes minicolumnar RF organization in the somatosensory cortex. Note that as an electrode penetration moves tangentially across a field of cortical macrocolumns (note locations of penetrations 1-30), the receptive field center (indicated on the digit tips to the right of the cortical field) moves a significant distance only after crossing a macrocolumnar border. While within the macrocolumn, the receptive field centers remain relatively closely spaced. It is also of note that the receptive field properties are constrained within the radial dimension; that is, if the electrode is moved along the radial dimension (note the penetrations denoted a-g), the receptive field center does not shift and receptive field proper-

http://dx.doi.org/10.5772/54801

ties will be very similar. As the description above is over-simplified, it should be noted that there is a great diversity of receptive field properties between neighboring minicolumns, and a stimulus that effectively activates one minicolumn will often be ineffective at activating that minicolumn's nearest neighbor [9-10]

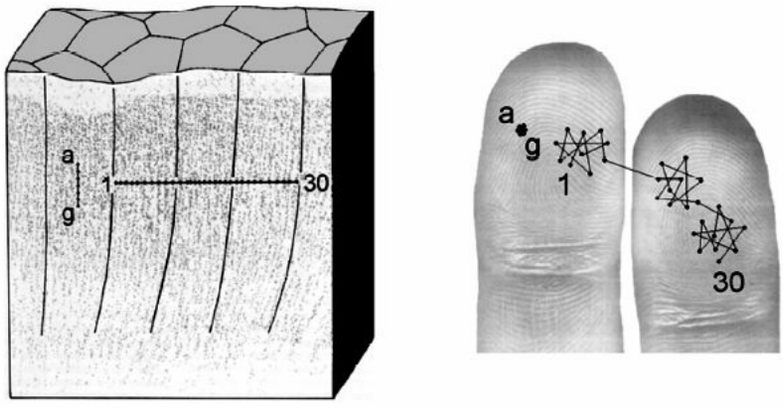

Figure 1. Summary of minicolumnar RF organization in SI somatosensory cortex. Left: Drawing of cross-section of Nissl-stained cortical tissue showing darkly-stained cell bodies organized in radially oriented cords, interpreted as minicolumns. Filled circles labeled *a–g*—sequence of neurons located within a single minicolumn; *1–30*—sequence of neurons located in series of adjacent minicolumns. Right: Sequences of RF centers (connected dots) mapped by neuron sequences *a–g* and *1–30*. Note that RF centers for SI neurons that occupy the same minicolumn stay close together, whereas the RF centers for pairs of neurons located in neighboring minicolumns shift back and forth over large distances, and occupy totally non-overlapping skin regions when the pair of neurons occupies different SI macrocolumns. Based on [8-10].

The findings and predictions by Favorov et al were later confirmed with additional data that was obtained via optical intrinsic signal imaging (for description of technique, see [11]). In this study, responses evoked by vibrotactile stimuli delivered to different positions on the skin (which differed by only the width of the 2mm probe tip) showed a subtle variation within the macrocolumnar pattern within a range of stimulus positions (analyzed with the methods described in [12]), but the global pattern did not shift until a new group of minicolumns (or macrocolumns) was stimulated. Figure 2 summarizes the results of one such imaging experiment in which the macrocolumnar pattern of cortical response does not significantly alter with a small shift in stimulus position until a border is crossed. Additional features of these minicolumnar patterns of activity that have been characterized are that they are stimulus magnitude- and duration-dependent [12-14]. For example, increasing the stimulus duration leads to more distinct and well-defined minicolumnar patterns of cortical activity. Additionally, the spectrum of the spatial profile of this activity evoked by the active minicolumns robustly and significantly shifts to lower frequencies, and the spectral shifts that have been observed are consistent with the concept of increased GABA mediated lateral inhibition between minicolumns [12]. Perceptually, these changes in minicolumnar activity patterns with stimulus duration could parallel the increases in sensory perception that have been observed with longer stimulus durations [15].

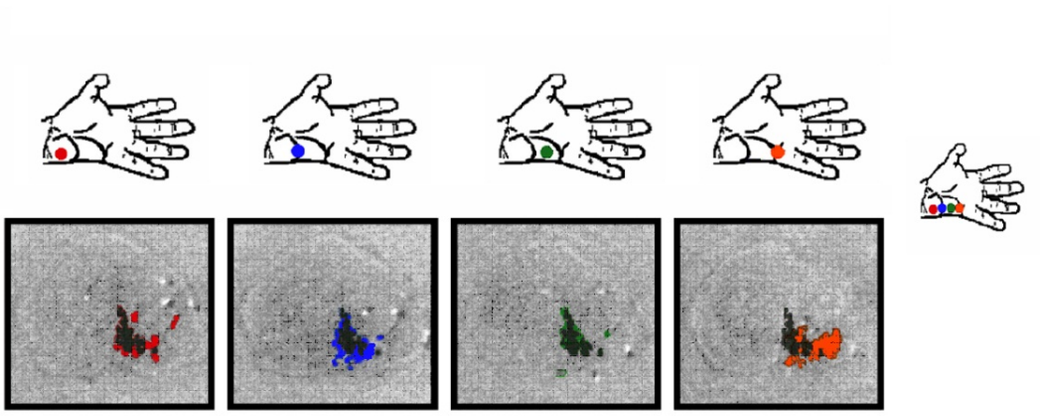

Figure 2. Summary of optical intrinsic signal evoked responses in SI cortex from four adjacent stimulus positions. Difference in stimulus position was equal to probe diameter (2 mm). Note the abrupt shift between the responses evoked from the stimulus placed at the first three positions vs. that of the fourth. Modified from [13].

Casanova and colleagues have demonstrated that there is a substantial increase in minicolumn density in the parietal cortex of individuals with autism [1,16]. This increase in minicolumn density results in a disproportionately large number of minicolumns becoming packed into the same cortical space and also results in a decrease in the neuropil between minicolumns. Thus, although there are now a higher density of minicolumns, there is less room for the GABA mediated lateral inhibitory connections between the minicolumns that are necessary for shaping the within-macrocolumn response that has been observed with repetitive stimulus duration [12-14, 17-20]. This alteration in basic cortical microarchitecture would then predictably contribute to an individual's sensory perception in a couple of ways. First, the increase in minicolumn density should afford an individual with autism an advantage in some sensory tasks, such as spatial localization, in which the percept would be improved. However, below baseline GABA mediated lateral inhibition between minicolumns would mean that increasing the duration of a stimulus would not increase the resolution or distinction of the within macrocolumn pattern of minicolumnar activity to the same degree, and thus, perception would not be improved. With this hypothesis of the minicolumn's role in spatial localization in mind, we designed an experiment to evaluate the differences between the spatial localization ability of neurotypical controls and subjects with autism [21]. In the study, a subject's ability to distinguish between two points on the skin (on the hand dorsum) was determined with two different stimulus durations – 500 msec and 5 sec (full description of the method in [21, 22]). Results from that study are summarized in Figure 3. Although individuals with autism outperformed controls in the shorter stimulus duration task, they did not demonstrate the nearly two-fold improvement that the controls did when the stimulus duration was extended. Thus, in the case of spatial localization, it appears that alterations in sensory percept could be accounted for by the changes that have been observed in cortical minicolumn architecture.

http://dx.doi.org/10.5772/54801

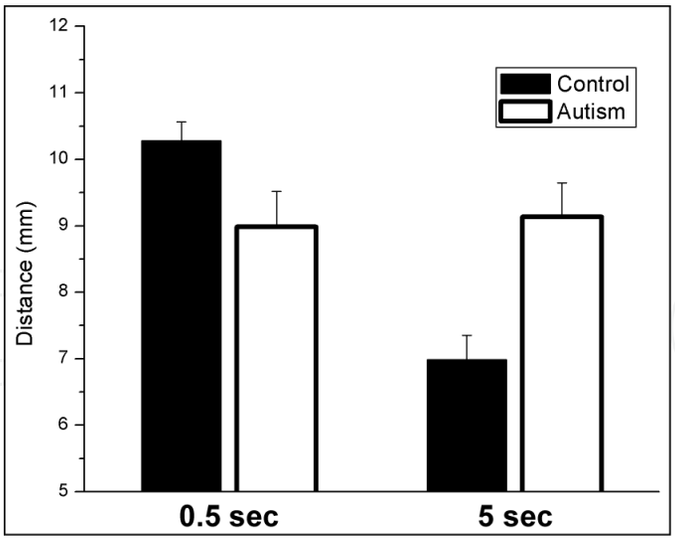

Figure 3. Spatial localization under two conditions of adapting stimulus duration for adults with autism versus neurotypical controls. Data displayed from the control subjects (previously reported [22]) contrasts markedly from the data obtained from observations of subjects with autism. Note that subjects with autism, although they clearly outperformed the controls in the 0.5 sec adapting condition, did not improve with the 5.0 sec adapting condition. Modified from [21]

The difference that was observed in short vs. long stimulus duration in the above-described spatial localization experiment led us to examine more directly the relationship between our previous adaptation animal studies and the role that adaptation – or conditioning stimulation – plays in sensory information processing in autism. It has been well established that conditioning stimulation – or prolonged pre-exposure to sensory stimulation – significantly modifies discriminative capacity and alters the ability of both peripheral and CNS neurons to process sensory information. Less widely appreciated is the fact that primary sensory cortical mechanisms undergo transient and significant alterations in response to repetitive sensory stimulation. Investigation of the dynamic cortical responses evoked by repetitive stimulation has been an ongoing line of research in our laboratory. One of the focal points has been the spatio-temporal patterns of response in the somatosensory cortex evoked by skin stimulation and how these patterns influence the cortical response to subsequent stimuli. For example, the observations of a number of studies have demonstrated that the spatially distributed pattern of activity evoked in SI cortex by cutaneous flutter stimulation exhibits a prominent time-dependency [11, 23, 24]. Specifically, changing the stimulus duration from 500 msec to 5 sec (such as was done in the spatial localization task described above) would result in two distinctly different patterns of response in SI cortex. Figure 4 compares the profiles of two SI cortical responses evoked by vibrotactile stimuli that differed only in duration (Note that the profile is a radial histogram of OIS images generated by plotting the cortical activity evoked by the stimulus as a function of the distance from the center of the region in SI that is maximally activated by the stimulus; [23, 24]). With the 500 msec stimulus, the entire response profile is above-background. However, with the longer duration 5 sec stimulus, a suppressive or inhibitory region surrounds the maximally activated region. This region of inhibitory influence – which persists for several seconds – would interfere with the SI response to a stimulus applied

concurrently or subsequently to skin regions in near proximity represented by neurons in that region of SI. Thus, in the case of the above-described spatial localization task, longer stimulus durations would be expected to improve performance. Since the presence of a center-surround in stimulus evoked cortical activity is commonly recognized as a function of GABA mediated pericolumnar lateral inhibition [25, 26], and a number of researchers have described GABA deficiency as being consistent with autism [27-31], we concluded that the lack of improvement with increasing stimulus duration in autism subjects in the spatial localization task could be due to a deficiency in GABA mediated neurotransmission.

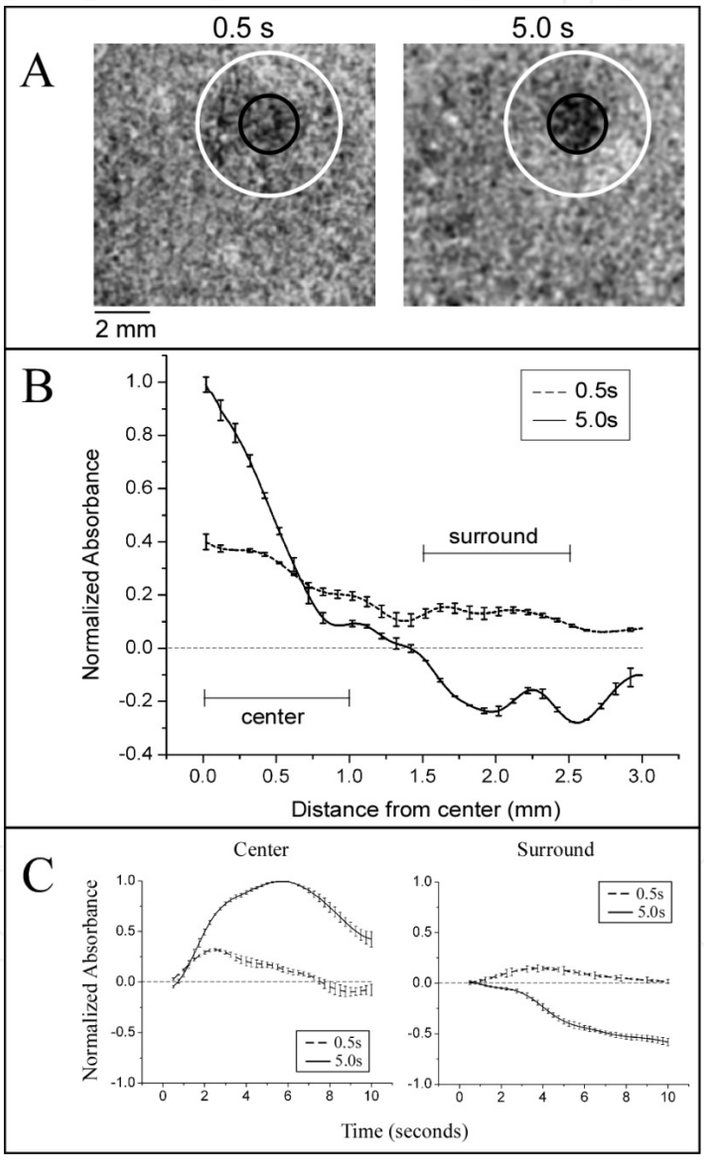

Figure 4. Radial histograms of SI cortical activity averaged across subjects (squirrel monkeys, *n* = 5). Cortical activity is measured in terms of light absorbance (increased light absorbance can be correlated to increased cortical activity, for review, see [11]). Data from the center of the plot corresponds to the maximally responding SI cortical territory to the 5 sec stimulus condition. Note that at the 0.5 sec stimulus duration, there is no below-background activity. Modified from [23].

http://dx.doi.org/10.5772/54801

The improvements that are normally observed with extended stimulus durations could be attributed to stimulus-evoked inhibition that surrounds areas of excitation. Single unit studies and imaging studies using voltage-sensitive dyes likewise have shown that excitation in the responding neuronal population is accompanied by the development of a surrounding field of inhibition [32-35]. Similarly, imaging studies that have used the OIS have shown that prolonged stimulation of a discrete skin site not only is associated with increased absorbance within the SI region representing the stimulated skin site, but also with decreases in absorbance in surrounding regions [23, 36-38]. Regions of decreased absorbance (increased reflectance) such as that described in Figure 4 are widely believed to be indicative of decreases in neuronal spike discharge activity [39-41], possibly resulting from stimulus-evoked inhibition at these locations. Thus, there is a great deal of evidence that the suppressed or below-background activity observed suggests that stimulus-evoked inhibition is responsible for the improvements in performance that are normally observed with repetitive stimulation. However, it appears that in the case of autism, there is sufficient evidence to speculate that the normal center-surround relationship in cortical patterns of activity does not fully develop.

3. Cortical modularity and adaptation

In addition to changes in spatial contrast, as described above, repetitive stimulation also results in temporally defined changes of cortical activity, the most prominent of which is a reduction in cortical response with extended stimulus duration. At the single cell level, both visual and somatosensory cortical pyramidal neurons undergo prominent use-dependent modifications of their receptive fields and response properties with repetitive stimulation. These modifications can attain full development within a few tens of milliseconds of stimulus onset, and can disappear within seconds after the stimulus ends (visual cortical neurons: [42-53]) alternatively – for review of short term cortical neuron dynamics in visual cortex, see [53, 54]; for review of short-term primary somatosensory cortical neuron dynamics see [15, 55].

Optical imaging studies have also characterized the short-term dynamics of the population-level response of squirrel monkey contralateral primary somatosensory (SI) cortex using different amplitudes and durations of vibrotactile stimulation [11, 12, 23, 24, 56]. The results of these optical intrinsic signal (OIS) imaging studies demonstrated a strong correlation between the amplitude of 25 Hz vibrotactile (flutter) skin stimulation and the response magnitude evoked in SI. In addition to the systematic changes in the spatial pattern of response in SI that correlated with increases in the amplitude and the duration of the stimulus, increasing the stimulus duration led to differences not only in the peak magnitude of the evoked cortical response, but also in the relative rates of rise and decay of the magnitude of the evoked intrinsic signal. These differences in the rates of rise and decay could impact the refractory period following a stimulus during which the magnitude of the response to a subsequent stimulus is diminished [57].

In order to assess the impact that adaptation has on perception, experiments were designed to directly measure the change in amplitude discrimination capacity that occurs with prior

stimulus exposure (or prior conditioning stimuli). The studies demonstrated that a subject's ability to discriminate between two simultaneously delivered vibrotactile stimuli – differing only in amplitude and location – was very robust and repeatable across a large number of (healthy) subjects but was very sensitive to varying conditions of pre-exposure to sensory stimuli [58]. Changing the duration of the conditioning stimulus delivered to one of the two sites before the amplitude discrimination task significantly altered a subject's ability to determine the actual difference between the two stimuli. One significant finding of that study was that specific durations of conditioning stimuli altered the subject's amplitude discriminative capacity in a predictive and quantifiable fashion (see Figure 5).

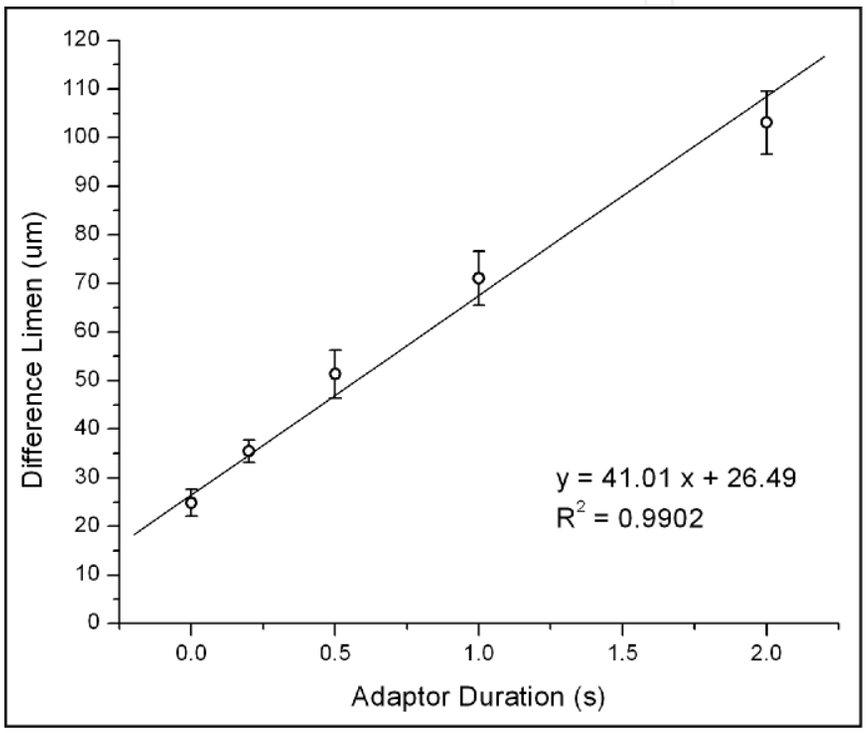

Figure 5. Comparison of amplitude difference threshold (with s.e. bars) to different conditions of adaptation. The test and standard stimuli were preceded by an adapting stimulus at the site of the test stimulus (ranging from 0.2 to 2 sec in duration). Note that single site adapting stimulation leads to a progressive and systematic decrease in performance with increasing adaptor duration [58].

This finding indicated that the method could be viewed as a reliable indicator of the influence of adapting stimuli on cortical response, as changes in peripheral response are not mediated at these short stimulus durations (for discussion, see [58]).

Conditioning stimuli did not have as pronounced an impact on the amplitude discriminative capability of subjects with autism as it did with the control group [60]. In Figure 6, results obtained using identical methods from subjects with autism and controls are compared. Note that adaptation (i.e., a 1 sec conditioning stimulus at one stimulus site prior to the amplitude discrimination task) resulted in the control subjects performing significantly worse than they did in the absence of adaptation. However, in the case of the autism subjects, the impact of

http://dx.doi.org/10.5772/54801

prior history of stimulation was not as significant, and the amplitude discrimination metric was not impacted to the same degree as it was in the controls. Thus, the ineffectiveness of a conditioning stimulus in this study repeated the findings of the spatial localization studies, in that adapting stimuli had little or diminished effect – positive or negative – on the sensory discriminative performance of individuals with autism.

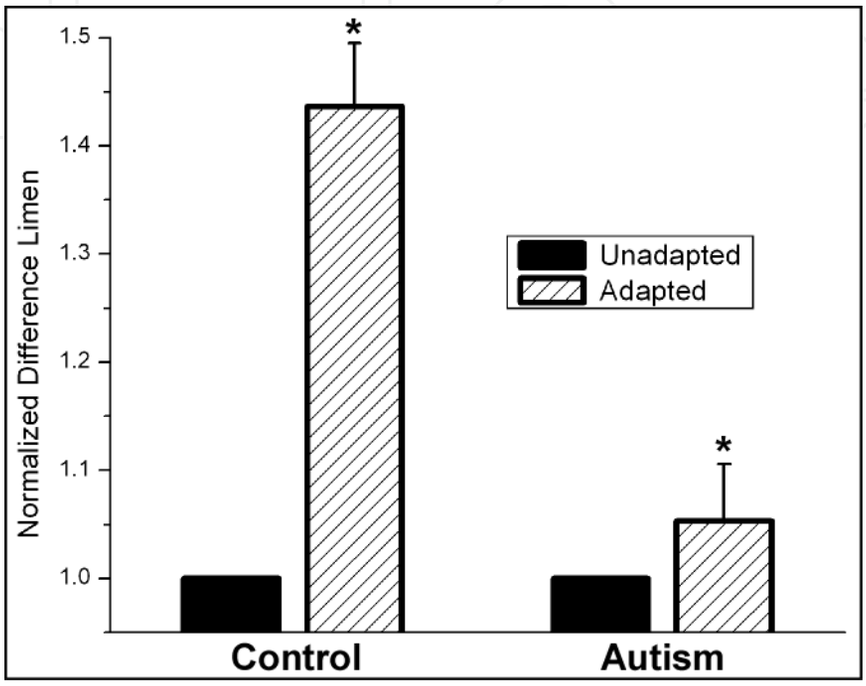

Figure 6. Comparison of difference limen (with s.e. bars) normalized to the unadapted condition. Note that for both the control and the autism group, 1 sec adaptation resulted in an elevated difference limen (* ANOVA; $p < 0.01$). The control group showed a greater impairment with adaptation (~45%) than the autism group (~5%) [59].

4. Cortical modularity and synchronization

There are a number of autism studies that have described Parkinsonian-like motor characteristics and/or postural control problems, which could be attributed to deficits of the basal ganglia portion of the frontostriatal system [60, 61]. These deficits in sensorimotor control could be derived, in part, from the role that the frontostriatal system plays in an individual's timing perception as well as the coordination that is required between cortical regions during sensorimotor tasks. Timing perception, which can be measured with some relatively simple temporal discriminative measures (such as TOJ: temporal order judgment and TDT: temporal discriminative threshold) – is most often accounted for by the frontostriatal system largely as a result of these measures being sensitive to lesions to the supplementary motor area (SMA), posterior parietal cortex, and basal ganglia [62, 63]. Also because of the fact that above-average TOJ thresholds occur in subjects with known damage to these same cortical areas (dyslexia [64], dystonia [65-67] and Parkinson's disease [68]). Most recently, it was found that individuals

with autism also have below-average timing perception capacity [69]. This timing deficit could be accounted for by differences in a number of structures, particularly in the frontostriatal system, that have been implicated in autism (e.g., basal ganglia [70-76]; caudate nucleus [70]; thalamus [77, 78]; and impaired white matter connectivity in the frontal lobe [79]).

In addition to the role that the frontostriatal system may have in the perceptual timing deficits of autism, the role of synchronization (or lack of synchronization) in autism has gained a certain degree of prominent attention. Uhlhaas and Singer [80] recently reviewed the experimental evidence that suggests that functional connectivity is reduced in autism, primarily based on fMRI studies [81-86] that examine the coordinated activity between different areas of the cerebral cortex. A few studies, using MEG and EEG, have found gamma oscillations, which are considered to be important in the process of coordinating cortical activity, to be below normal in subjects with autism [87, 88]. From the perspective of cortical modularity at both the minicolumnar and macrocolumnar scales, synchronization at the local cortical level should also be impacted. Casanova and colleagues have suggested that the aberrant minicolumnar structure that they have found in autism could result in the disruption of the inhibitory architecture [16] that is required for normal function in local neural circuitry. Disruption of functional connectivity at the local minicolumnar level could be responsible for, or strongly correlated with, the dysfunctional connectivity that has been observed across large-scale cortical areas.

There is a rapidly growing appreciation in neurobiological research of the important contributions to sensorimotor function of coordinated across-neuron patterns of spike discharge activity within the neocortical areas activated by sensory stimuli (for comprehensive review see [89]). In particular, stimulus-induced, time-dependent (dynamic) across-neuron synchronization of action potential discharge and the associated oscillatory modulation of spike firing are common and prominent properties of neocortical networks devoted to the processing of sensory information. The tendency of sensory neocortical networks to generate synchronized oscillations in response to stimulation has raised the possibility that synchronization may play a prominent role in some aspects of sensory perception. We examined whether or not synchronization could impact the topography of temporal perception [90]. The goal of the study was to elucidate the impact of stimulus-driven synchronization on adjacent cortical ensembles and the spatio-temporal integration of information that results from those ensembles being temporally linked or bound by a common synchronizing input. More specifically, we demonstrated that temporal order judgment (TOJ – a measure obtained from determining the minimal inter-stimulus interval necessary for a subject to detect the temporal order of two sequentially delivered peripheral stimuli) and temporal discrimination threshold (TDT) in neurotypical subjects were significantly impacted when two synchronized (but low amplitude) vibrotactile stimuli were delivered concurrently to the dual test stimulus sites. The conclusion of that study was that the stimulus-driven linkage between topographically adjacent sites resulted in an increase in TOJ threshold and TDT (or worse performance), most likely because these cortically adjacent or near-adjacent regions were being driven with a simultaneous and identical sinusoidal pair of tactile stimuli which contributed to a loss in spatio-temporal contrast [90].

http://dx.doi.org/10.5772/54801

A subsequent question that was then addressed was whether or not individuals with autism experience a decrease in timing perception (as measured by TOJ and TDT) if the same concurrent synchronizing stimuli were delivered during the TOJ/TDT tests. If neurologically compromised individuals – such as those with autism – have distinct systemic cortical deficits, and these deficits extend to local neuronal circuitry connectivity, then the abnormal functional connectivity between adjacent and/or near adjacent cortical ensembles would hypothetically decrease the effect that stimulus-driven synchronization has on the TOJ or TDT task (i.e., performance on the task would not degrade). Comparisons of the control vs. autism results (previously reported in [69, 90]) are shown in Figure 7. Note that with concurrent stimulation, individuals with autism do not suffer the same decrease in sensory discriminative performance that controls do. In other words, the functional linkage in controls that becomes rapidly established, due to local synchronization effects, appears to perceptually bind the two stimulus sites (in this case, digits two and three) to an extent that it becomes more difficult to identify the temporal order between the two sites. Thus, as in the case of adaptive responses, it appears that there is a loss of an ability to integrate both spatial and temporal information in autism.

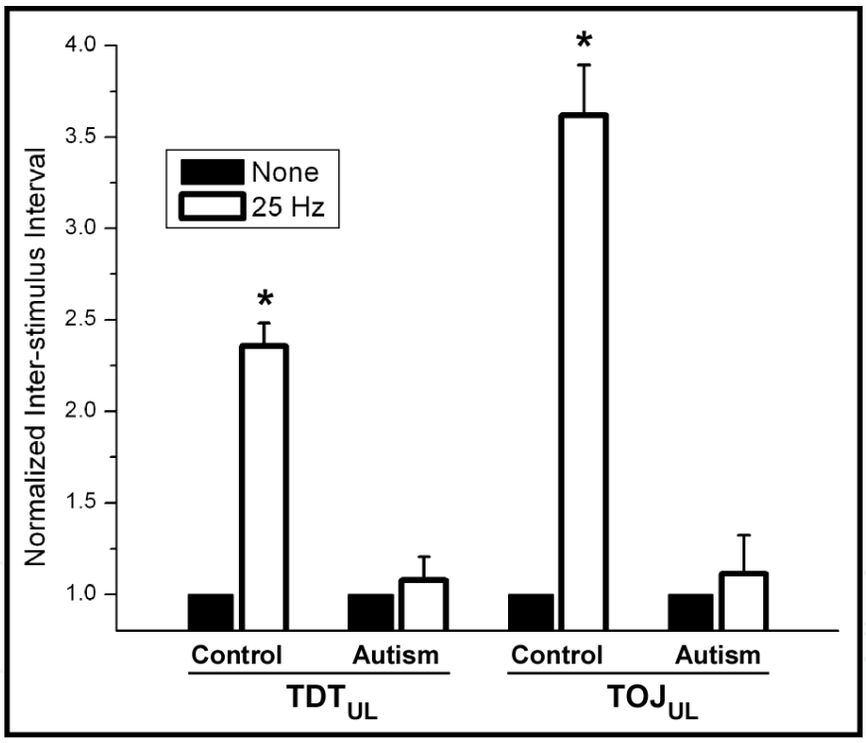

Figure 7. TDT and TOJ performance metrics obtained in the presence and absence of 25 Hz conditioning stimulation. The 25 Hz conditioning stimulus significantly impaired TDT by ~240% ($p < 0.01$) and TOJ by ~360% ($p < 0.01$) for the control group, whereas the autism group showed no significant change for either measure [69].

What could account for the reduction in TOJ performance in Typically Developing (TD) controls? Functional connectivity between neighboring cortical regions normally leads to a reduction in TOJ performance in healthy controls with the introduction of the synchronized conditioning stimuli, and this is predicted by recordings from *in vivo* animal studies. Consider

the results displayed in Figure 8. Extracellular recordings were obtained from SI cortical regions corresponding to D2 and D3 in the squirrel monkey. When a vibrotactile pulse was delivered to D2, a significant above background response was evoked at D2 (top left quadrant) but not at the D3 representation (top right quadrant). However, when sub-threshold synchronized sinusoidal stimuli were delivered to both digits prior to the pulse (bottom half of Figure 8), the pulse at D2 evokes a response at both the D2 and D3 representations (note absence of evoked activity before zero msec during subthreshold stimulation).

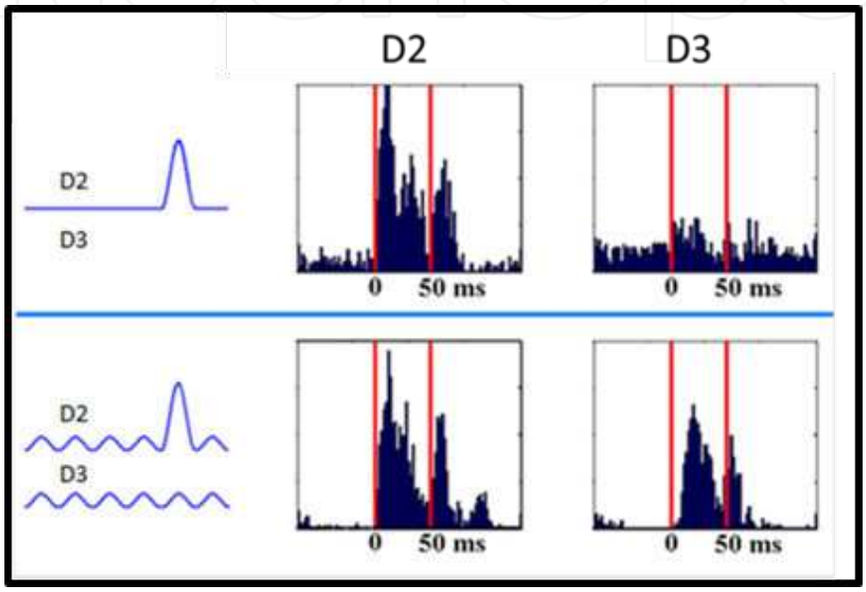

Figure 8. Extracellular recordings obtained from SI cortical regions corresponding to D2 and D3 in the squirrel monkey. When a vibrotactile pulse was delivered, a significant above background response was evoked at D2 but not at the D3 representation. When sub-threshold synchronized sinusoidal stimuli were delivered to both digits prior to the pulse, the pulse at D2 evokes a response at both the D2 and D3 representations.

From this type of data, we hypothesized that this response was the result of functional connectivity between adjacent and/or near adjacent cortical ensembles. In other words, the conditioning stimuli delivered prior to the TOJ task engaged the cortical ensembles in the D2 and D3 cortical representations to be in concert, and delivery of a simple stimulus to one digit (D2) resulted in a near simultaneous response at the representation of another digit (D3). Thus, it would be predicted that delivery of synchronized conditioning stimuli would impact the topography of temporal perception [90]. However, individuals with autism do not suffer the same decrease in sensory discriminative performance that neurotypical controls do. In other words, the functional linkage that becomes rapidly established in TD individuals to local synchronization effects. appears to perceptually bind the two stimulus sites does not occur in autism [69]. Thus, an extrapolation of this is that, utilizing measures impacted by stimulus driven synchronization, there is significant hypo-connectivity in autism at the level of local cortical ensembles.

http://dx.doi.org/10.5772/54801

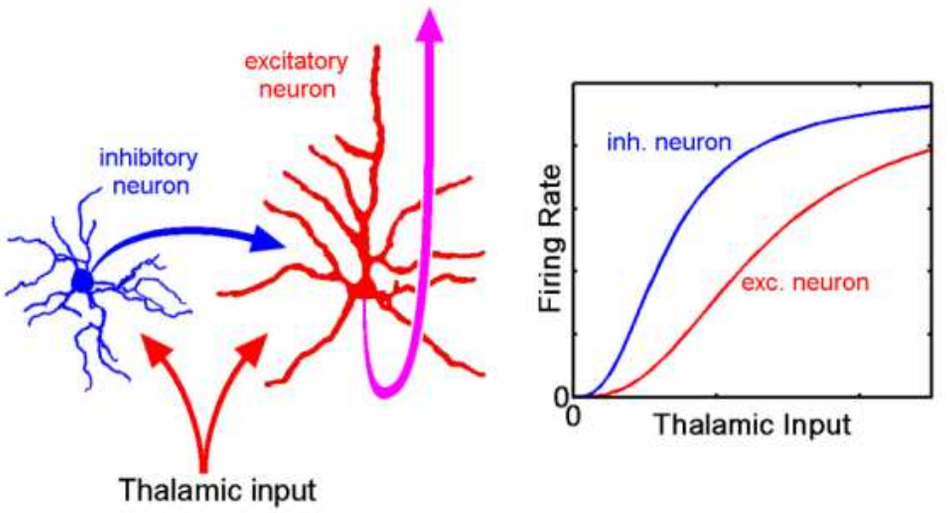

Figure 9. Visual representation of feed forward inhibition

Interim Summary: In the previous 3 sections, we described sensory-based diagnostic protocols that were based on neurophysiological principles that have been elucidated in animal studies. In the following sections, we describe additional protocols based on hypotheses that have not yet been tested in *in vivo* animal models, and it is anticipated that these protocols will add further insight into differences in fundamental mechanisms of information processing between TD and Autism Spectrum Disorder (ASD) individuals.

5. The role of sub-threshold stimulus-evoked inhibition: feed-forward inhibition and the role of within-column connectivity

A major well-documented feature of cortical functional organization is the presence of prominent feed-forward inhibition in the input layer 4 (see Figure 9). Local layer 4 inhibitory cells receive direct thalamocortical input and in turn suppress responses of neighboring layer 4 excitatory cells to their thalamocortical drive, thereby sharpening their RF properties [91-96]. These inhibitory cells are more responsive to weak (near-threshold) afferent drive than are the excitatory layer 4 cells and thus they *raise* the threshold at which excitatory layer 4 cells begin to respond to peripheral stimuli. Sensory testing of stimulus detection threshold is particularly well-suited for probing feed-forward inhibition, considering that stimuli just below the detection threshold will be too weak to vigorously engage other layer 4 mechanisms besides thalamocortical excitation and feed-forward inhibition (such as lateral excitation, recurrent or feedback inhibition, or activity-driven adaptation).

Tactile thresholds were collected in two distinct manners. The "static thresholds were measured using a 20-trial Two Alternative Forced Choice (2AFC) Tracking protocol. During each trial a 25 Hz vibrotactile test stimulus (lasts 500 ms) was delivered to either D2 or D3; the stimulus location was randomly selected on a trial-by-trial basis. Following each vibrotactile

stimulus, the subject was prompted to select the skin site (D2 vs. D3) that perceived the stimulation. After a 5sec delay – based on subject response – the stimulation was repeated until the completion of the 20 trials. The stimulus amplitude was started at 15μm and was modified based on the subject's response in the preceding trial. During the "dynamic" threshold detection, a 25 Hz vibrotactile stimulus was delivered to either D2 or D3 (the stimulus location was randomly selected on a trial-by-trial basis). The amplitude of the stimulus was initiated from zero and increased in steps of 2 μm/s. The subject was instructed to indicate the skin site that received the stimulus as soon as the vibration was detected. Multiple trials were conducted with a random delay between trials and the results from those trials were averaged for each subject. For a complete experimental explanation, see [97-99].

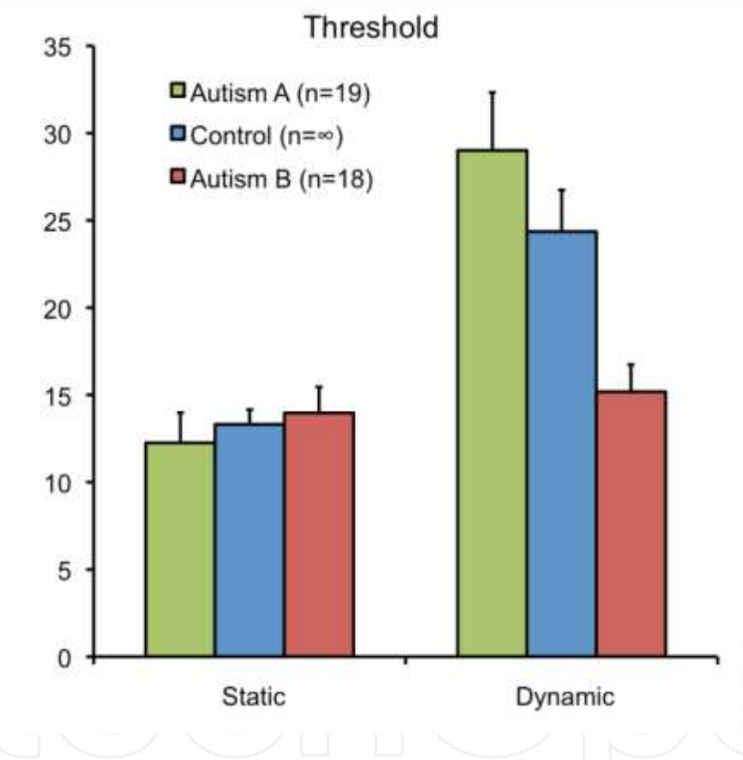

Figure 10. Static Thresholds collected using a 2AFC Protocol are compared to Dynamic Thresholds using a ramping amplitude protocol.

In our comparative study of typically developing vs. autism individuals, we found that subjects with autism exhibit significantly greater diversity in their detection thresholds on fingertips than control subjects, with two groups emerging (designated as Group A and Group B). Based on cluster analysis of several measures, the data that we have obtained thus far strongly suggests two distinct clusters within the spectrum. Group B autism individuals have dynamic thresholds lower than controls (thus suggesting reduced feed-forward inhibition) and group A autism individuals have dynamic thresholds higher than controls (thus suggest-

http://dx.doi.org/10.5772/54801

ing enhanced feed-forward inhibition). Inhibitory neurogliaform cells in layer 4 use both $GABA_A$ and $GABA_B$ receptor-mediated inhibitory synaptic transmission ([100]; in other inhibitory cell classes, $GABA_B$ receptors are located in the presynaptic membrane and used for autocontrol). $GABA_B$-mediated inhibition develops and lasts much longer than $GABA_A$-mediated inhibition. We believe we detect the $GABA_B$ component of feed-forward inhibition in our new "dynamic:" variant of the basic ("static") detection threshold test, in which we deliver vibrotactile stimuli of gradually increasing amplitude (starting at zero and growing at a rate of 2 μm/s) until the subject detects the vibration. Interestingly, this time-extended mode of stimulus delivery prominently elevates the detection threshold (compare "static" and "dynamic" plots in Figure 10), presumably by fully activating slow $GABA_B$ inhibition in addition to fast $GABA_A$ inhibition. Again we find that autism subjects exhibit greater diversity on this test than controls: group A autism individuals have static thresholds below controls, but dynamic thresholds above controls (suggesting reduced $GABA_A$ inhibition, but elevated $GABA_B$ inhibition), while group B autism have the opposite relations. Thus, if alteration of GABAa vs. GABAb inhibition influences the impact of subthreshold mediated activation, then the two aforementioned autism populations should, if treated pharmacologically, respond differently to a GABAb agonist, such as baclofen. If this is the case, then a simple measure such as that described above could predict whether or not this particular treatment would be effective.

6. Temporal integration: Rate dependent modulation of vibrotactile stimuli

The difference that we observed with static vs. dynamic thresholds encouraged us to explore the impact that changing the rate of amplitude modulation would have on sensory percept performance at supra-threshold levels. In the dynamic threshold task, an amplitude modulation rate of 2 μm/s was used to deliver a *subthreshold* stimulus. Delivering higher rates of amplitude modulation at above threshold values yields very different results. In the data presented below, a subject's ability to match two stimuli was assessed at nine different rates of amplitude modulation (one stimulus was held at steady state values, the other was increased until it was perceived as a match; [99]). At the lowest rates, subjects performed comparably to the dynamic threshold task (Autism group A performed worse than controls and Autism B, though not significantly). With an increasing rate of modulation, from 1.25 to 10 μm/s, the Autism A group demonstrated a decreasing Difference Limen (DL). As the rate increased above 15 μm/s ond, this group began performing significantly worse in that the test stimuli was increased well beyond the value of the standard stimulus (resulting in the "negative" DL). It appears that this group was unable to temporally integrate information from the stimuli, and future in vivo studies will examine the role that different neurotransmitter systems play in such temporal integration.

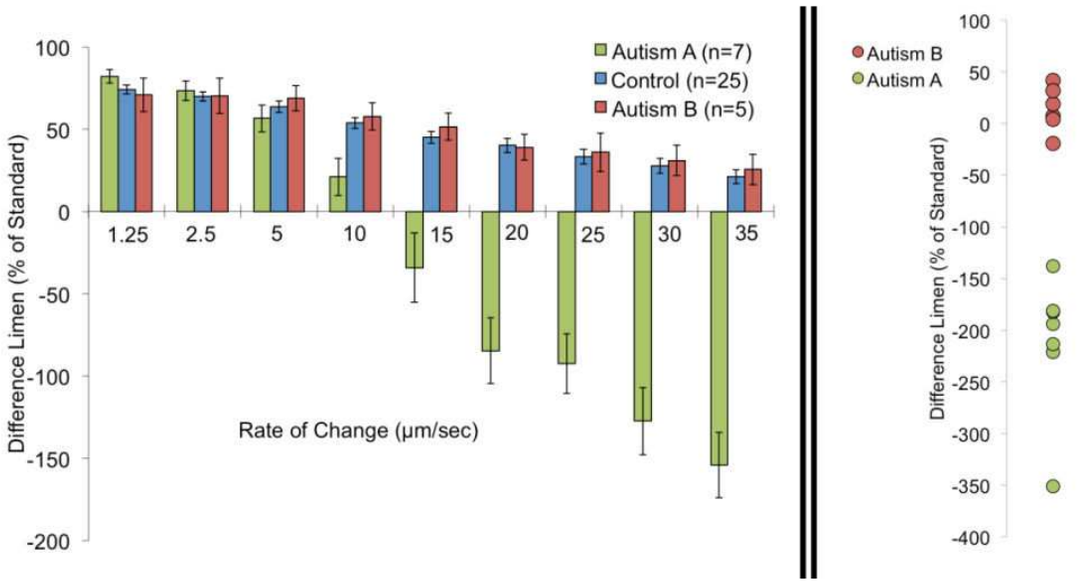

Figure 11. Left Panel: Comparison of data obtained from typically developing controls vs. individuals with autism. Note that at lower rates of stimulus amplitude modulation, all 3 groups behave approximately the same way. As the amplitude modulation rate is increased, the responses of one of the autism groups diverge distinctly from the responses of the other subjects. Note that the negative Weber fraction indicates that the subject responded beyond the matching point of the two stimuli rather than before. Right Panel: Comparison of individual data points from the highest modulation rate displayed in Panel A. Note the clustering of the data points within each of the groups of subjects.

7. Generating an individual CNS profile from multiple measures

A battery of protocols yields multiple parameters that can be used to build a CNS profile of a subject. Since each of the tests are influenced by some mechanisms more than others (e.g., adaptation will influence the evoked cortical response during conditioning prior to a TOJ task, but synchronization of cortical ensembles appears to have the predominant outcome on that task), combining the results from multiple tasks – with each task characterized as an independent vector of performance for some aspect of CNS information processing - would predictably yield a unique individual CNS profile. To fully appreciate the differences between subject populations, we utilized a modern mathematical approach for multi-variable analysis. Quantitative performance of each subject on the battery of *N* sensory tests was treated as localizing a subject in an *N*-dimensional "cortical metrics" space (i.e., an abstract space in which each coordinate axis corresponds to one of the battery's sensory tests). Principal Component Analysis (PCA) was then used to graphically display the test-performance data collected in the different subject populations. Figure 12, for example, was generated using PCA on 8 metrics, and it clearly separates individuals with autism (orange) from TD controls (blue) with a 99% confidence level that the two populations are different (using a t-squared Hotelling test). Our long term goal with this work is to develop metrics that have the requisite sensitivity to reflect the impact that treatments or interventions have. It is anticipated that successful treatments would result in a shift of the autism values towards the more tightly clustered control values.

http://dx.doi.org/10.5772/54801

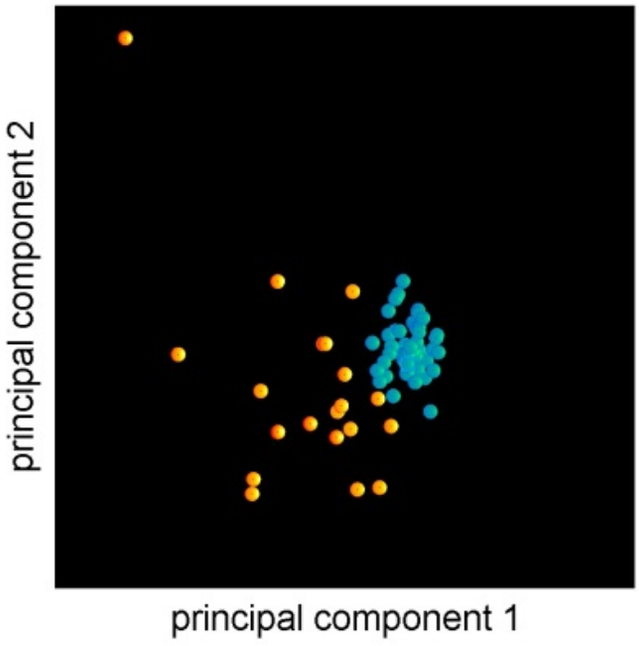

Figure 12. PCA Analysis was used to examine the performance of two populations on 8 differerent metrics. The analysis clearly separates individuals with autism (orange) from TD controls (blue). (99% confidence using a t-squared Hotelling test)

8. Conclusions

Adults with autism exhibit inhibitory deficits that are often manifested in behavioral modifications such as repetitive behaviors and/or sensory hyper-responsiveness. If such behaviors are the result of a generalized deficiency in inhibitory neurotransmission, then it stands to reason that deficits involving localized cortical-cortical interactions – such as in sensory discrimination tasks – could be detected and quantified. This chapter describes recently developed hypothesis driven methods for quantifying metrics of sensory perception based on the neurophysiological principles of cortical modularity. These novel sensory discrimination tests may provide (a) an effective means for biobehavioral assessment of deficits specific to autism and (b) efficient and sensitive measures of change following treatment. The methods could prove to be a useful and efficient way to detect specific neural deficits and monitor the efficacy of pharmacological and/or behavioral treatments in autism.

Author details

Eric Francisco, Oleg Favorov and Mark Tommerdahl

Biomedical Engineering University of North Carolina at Chapel Hill Chapel Hill, NC, USA

References

[1] Casanova, M. F, Buxhoeveden, D. P, Switala, A. E, & Roy, E. Minicolumnar pathology in autism. Neurology (2002). , 58, 428-32.

[2] Mountcastle, V. B. In: Edelman GM, Mountcastle VB, editors. The Mindful Brain. Cambridge, MA: MIT Press; (1978). , 51-100.

[3] Rakic, P. Specification of cerebral cortical areas. Science (1988). , 241, 170-6.

[4] Peters, A, & Yilmaz, E. Neuronal organization in area 17 of cat visual cortex. Cereb Cortex (1993). , 3, 49-68.

[5] Jones, E. G. Varieties and distribution of non-pyramidal cells in the somatic sensory cortex of the squirrel monkey. J Comp Neurol (1975). , 160, 205-67.

[6] Jones, E. G. Anatomy of cerebral cortex: columnar input-output organization. In: Schmitt FO, editor. The Organization of the Cerebral Cortex. Cambridge, MA: MIT Press; (1981). , 199-235.

[7] Lund, J. S. Spiny Stellate Neurons. In: Jones EG, editor. Cerebral Cortex. New York: Plenum Press; (1984). , 255-308.

[8] Favorov, O. V, & Diamond, M. E. Demonstration of discrete place-defined columns--segregates--in the cat SI. J Comp Neurol (1990). , 298, 97-112.

[9] Favorov, O, & Whitsel, B. L. Spatial organization of the peripheral input to area 1 cell columns. I. The detection of'segregates'. Brain Res (1988). , 472, 25-42.

[10] Favorov, O. V, & Kelly, D. G. Minicolumnar Organization within Somatosensory Cortical Segregates: I. Development of Afferent Connections. Cereb Cortex (1994). , 4(4), 408-427.

[11] Tommerdahl, M, Favorov, O, & Whitsel, B. L. Optical imaging of intrinsic signals in somatosensory cortex. Behav Brain Res (2002). , 135, 83-91.

[12] Chiu, J. S, Tommerdahl, M, Whitsel, B. L, & Favorov, O. V. Stimulus-dependent spatial patterns of response in SI cortex. BMC Neurosci (2005).

[13] Chiu, J. Characterization of Minicolumnar Patterns in SI Cortex [Dissertation]. Chapel Hill: University of North Carolina at Chapel Hill; (2006).

[14] Tommerdahl, M, Chiu, J, Whitsel, B. L, & Favorov, O. Minicolumnar patterns in the global cortical response to sensory stimulation. In: Casanova MF, editor. Neocortical Modularity and the Cell Minicolumn. Hauppauge, New York: Nova Science Publishers, (2005).

[15] Tommerdahl, M, Favorov, O. V, & Whitsel, B. L. Dynamic representations of the somatosensory cortex. Neurosci Biobehav Rev. [Review]. (2010). Feb;, 34(2), 160-70.

[16] Casanova, M. F, Buxhoeveden, D, & Gomez, J. Disruption in the inhibitory architecture of the cell minicolumn: implications for autisim. Neuroscientist. (2003). Dec;, 9(6), 496-507.

[17] Tommerdahl, M, Whitsel, B. L, Cox, E. G, Diamond, M. E, & Kelly, D. G. Analysis of the periodicities in somatosensory cortical activity patterns. Society for Neuroscience Abstracts. (1987).

[18] Tommerdahl, M, Favorov, O, Whitsel, B. L, Nakhle, B, & Gonchar, Y. A. Minicolumnar activation patterns in cat and monkey SI cortex. Cereb Cortex. (1993). Sep-Oct;, 3(5), 399-411.

[19] Mccasland, J. S, & Woolsey, T. A. High-resolution 2-deoxyglucose mapping of functional cortical columns in mouse barrel cortex. The Journal of comparative neurology. (1988). Dec 22;, 278(4), 555-69.

[20] Kohn, A, Metz, C, Quibrera, M, Tommerdahl, M. A, & Whitsel, B. L. Functional neocortical microcircuitry demonstrated with intrinsic signal optical imaging in vitro. Neuroscience. (2000). , 95(1), 51-62.

[21] Tommerdahl, M, Tannan, V, Cascio, C. J, Baranek, G. T, & Whitsel, B. L. Vibrotactile adaptation fails to enhance spatial localization in adults with autism. Brain Res. (2007). Jun 18;, 1154, 116-23.

[22] Tannan, V, Whitsel, B. L, & Tommerdahl, M. A. Vibrotactile adaptation enhances spatial localization. Brain Res. (2006). Aug 2;, 1102(1), 109-16.

[23] Simons, S. B, Tannan, V, Chiu, J, Favorov, O. V, Whitsel, B. L, & Tommerdahl, M. Amplitude-dependency of response of SI cortex to flutter stimulation. BMC Neurosci. (2005).

[24] Simons, S. B, Chiu, J, Favorov, O. V, Whitsel, B. L, & Tommerdahl, M. Duration-dependent response of SI to vibrotactile stimulation in squirrel monkey. Journal of neurophysiology. (2007). Mar;, 97(3), 2121-9.

[25] Juliano, S. L, Dusart, I, & Peschanski, M. Somatic activation of thalamic neurons transplanted into lesioned somatosensory thalamus. Brain Res. (1989). Jan 30;, 478(2), 356-60.

[26] Kohn, A, Metz, C, Quibrera, M, Tommerdahl, M. A, & Whitsel, B. L. Functional neocortical microcircuitry demonstrated with intrinsic signal optical imaging in vitro. Neuroscience. (2000). , 95(1), 51-62.

[27] Hussman, J. P. Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. Journal of autism and developmental disorders. (2001). Apr;, 31(2), 247-8.

[28] Blatt, G. J. GABAergic cerebellar system in autism: a neuropathological and developmental perspective. International review of neurobiology. (2005). , 71, 167-78.

[29] Casanova, M. F, Buxhoeveden, D, & Gomez, J. Disruption in the inhibitory architecture of the cell minicolumn: implications for autisim. Neuroscientist. (2003). Dec;, 9(6), 496-507.

[30] Belmonte, M. K, & Cook, E. H. Jr., Anderson GM, Rubenstein JL, Greenough WT, Beckel-Mitchener A, et al. Autism as a disorder of neural information processing: directions for research and targets for therapy. Mol Psychiatry. [Review]. (2004). Jul;, 9(7), 646-63.

[31] Chao, H. T, Chen, H, Samaco, R. C, Xue, M, Chahrour, M, Yoo, J, et al. Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature (2010). Nov 11;, 468(7321), 263-9.

[32] Brumberg, J. C, Pinto, D. J, & Simons, D. J. Spatial gradients and inhibitory summation in the rat whisker barrel system. Journal of neurophysiology. (1996). Jul;, 76(1), 130-40.

[33] Derdikman, D, Hildesheim, R, Ahissar, E, Arieli, A, & Grinvald, A. Imaging spatio-temporal dynamics of surround inhibition in the barrels somatosensory cortex. J Neurosci. (2003). Apr 15;, 23(8), 3100-5.

[34] Foeller, E, Celikel, T, & Feldman, D. E. Inhibitory sharpening of receptive fields contributes to whisker map plasticity in rat somatosensory cortex. Journal of neurophysiology. (2005). Dec;, 94(6), 4387-400.

[35] Wirth, C, & Luscher, H. R. Spatiotemporal evolution of excitation and inhibition in the rat barrel cortex investigated with multielectrode arrays. Journal of neurophysiology. (2004). Apr;, 91(4), 1635-47.

[36] Moore, C. I, Nelson, S. B, & Sur, M. Dynamics of neuronal processing in rat somatosensory cortex. Trends in neurosciences. (1999). Nov;, 22(11), 513-20.

[37] Tommerdahl, M, Whitsel, B. L, & Vierck, C. J. Jr., Favorov O, Juliano S, Cooper B, et al. Effects of spinal dorsal column transection on the response of monkey anterior parietal cortex to repetitive skin stimulation. Cereb Cortex. (1996). Mar-Apr;, 6(2), 131-55.

[38] Tommerdahl, M, Whitsel, B. L, Favorov, O. V, Metz, C. B, & Quinn, O. BL. Responses of contralateral SI and SII in cat to same-site cutaneous flutter versus vibration. Journal of neurophysiology. (1999). Oct;, 82(4), 1982-92.

[39] Grinvald, A. Real-time optical mapping of neuronal activity: from single growth cones to the intact mammalian brain. Annu Rev Neurosci. (1985). , 8, 263-305.

[40] Grinvald, A, Frostig, R. D, Siegel, R. M, & Bartfeld, E. High-resolution optical imaging of functional brain architecture in the awake monkey. Proceedings of the National Academy of Sciences of the United States of America. (1991). Dec 15;, 88(24), 11559-63.

[41] Whitsel, B. L, Kelly, E. F, Quibrera, M, Tommerdahl, M, Li, Y, Favorov, O. V, et al. Time-dependence of SI RA neuron response to cutaneous flutter stimulation. Somatosensory & motor research. (2003). , 20(1), 45-69.

[42] Bredfeldt, C. E, & Ringach, D. L. Dynamics of spatial frequency tuning in macaque J Neurosci. (2002). Mar 1;22(5):1976-84., 1

[43] Celebrini, S, Thorpe, S, Trotter, Y, & Imbert, M. Dynamics of orientation coding in area of the awake primate. Vis Neurosci. (1993). Sep-Oct;10(5):811-25., 1

[44] Das, A, & Gilbert, C. D. Receptive field expansion in adult visual cortex is linked to dynamic changes in strength of cortical connections. Journal of neurophysiology. (1995). Aug;, 74(2), 779-92.

[45] Deangelis, G. C, Anzai, A, Ohzawa, I, & Freeman, R. D. Receptive field structure in the visual cortex: does selective stimulation induce plasticity? Proceedings of the National Academy of Sciences of the United States of America. (1995). Oct 10;, 92(21), 9682-6.

[46] Dinse, H. R, & Kruger, K. Contribution of area 19 to the foreground-background-interaction of the cat: an analysis based on single cell recordings and behavioural experiments. Experimental brain research Experimentelle Hirnforschung. (1990). , 82(1), 107-22.

[47] Pack, C. C, & Born, R. T. Temporal dynamics of a neural solution to the aperture problem in visual area MT of macaque brain. Nature. (2001). Feb 22;, 409(6823), 1040-2.

[48] Pettet, M. W, & Gilbert, C. D. Dynamic changes in receptive-field size in cat primary visual cortex. Proceedings of the National Academy of Sciences of the United States of America. (1992). Sep 1;, 89(17), 8366-70.

[49] Ringach, D. L, Hawken, M. J, & Shapley, R. Dynamics of orientation tuning in macaque primary visual cortex. Nature. (1997). May 15;, 387(6630), 281-4.

[50] Shevelev, I. A, Eysel, U. T, Lazareva, N. A, & Sharaev, G. A. The contribution of intracortical inhibition to dynamics of orientation tuning in cat striate cortex neurons. Neuroscience. (1998). May;, 84(1), 11-23.

[51] Shevelev, I. A, Volgushev, M. A, & Sharaev, G. A. Dynamics of responses of neurons evoked by stimulation of different zones of receptive field. Neuroscience. (1992). Nov; 51(2):445-50., 1

[52] Sugase, Y, Yamane, S, Ueno, S, & Kawano, K. Global and fine information coded by single neurons in the temporal visual cortex. Nature. (1999). Aug 26;, 400(6747), 869-73.

[53] Kohn, A. Visual adaptation: physiology, mechanisms, and functional benefits. Journal of neurophysiology. (2007). May;, 97(5), 3155-64.

[54] Smith, M. A, & Kohn, A. Spatial and temporal scales of neuronal correlation in primary visual cortex. J Neurosci (2008). Nov 26;, 28(48), 12591-603.

[55] Kohn, A, & Whitsel, B. L. Sensory cortical dynamics. Behavioural brain research. (2002). Sep 20;135(1-2):119-26.

[56] Tommerdahl, M, Whitsel, B. L, & Vierck, C. J. Jr., Favorov O, Juliano S, Cooper B, et al. Effects of spinal dorsal column transection on the response of monkey anterior parietal cortex to repetitive skin stimulation. Cereb Cortex. (1996). Mar-Apr;, 6(2), 131-55.

[57] Cannestra, A. F, Pouratian, N, Shomer, M. H, & Toga, A. W. Refractory periods observed by intrinsic signal and fluorescent dye imaging. Journal of neurophysiology. (1998). Sep;, 80(3), 1522-32.

[58] Tannan, V, Simons, S, Dennis, R. G, & Tommerdahl, M. Effects of adaptation on the capacity to differentiate simultaneously delivered dual-site vibrotactile stimuli. Brain Res. (2007). Oct 22.

[59] Tannan, V, Holden, J. K, Zhang, Z, Baranek, G. T, & Tommerdahl, M. A. Perceptual metrics of individuals with autism provide evidence for disinhibition. Autism Res (2008). Aug;, 1(4), 223-30.

[60] Rinehart, N. J, Tonge, B. J, Bradshaw, J. L, Iansek, R, Enticott, P. G, & Mcginley, J. Gait function in high-functioning autism and Asperger's disorder: evidence for basal-ganglia and cerebellar involvement? European child & adolescent psychiatry. (2006). Aug;, 15(5), 256-64.

[61] Takarae, Y, Minshew, N. J, Luna, B, & Sweeney, J. A. Atypical involvement of frontostriatal systems during sensorimotor control in autism. Psychiatry research. (2007). Nov 15;, 156(2), 117-27.

[62] Lacruz, F, Artieda, J, Pastor, M. A, & Obeso, J. A. The anatomical basis of somaesthetic temporal discrimination in humans. Journal of neurology, neurosurgery, and psychiatry. (1991). Dec;, 54(12), 1077-81.

[63] Pastor, M. A, Day, B. L, Macaluso, E, Friston, K. J, & Frackowiak, R. S. The functional neuroanatomy of temporal discrimination. J Neurosci. (2004). Mar 10;, 24(10), 2585-91.

[64] Laasonen, M, Tomma-halme, J, Lahti-nuuttila, P, Service, E, & Virsu, V. Rate of information segregation in developmentally dyslexic children. Brain Lang. (2000). Oct 15;, 75(1), 66-81.

[65] Sanger, T. D, Tarsy, D, & Pascual-leone, A. Abnormalities of spatial and temporal sensory discrimination in writer's cramp. Mov Disord. (2001). Jan;, 16(1), 94-9.

[66] Tinazzi, M, Fiaschi, A, Frasson, E, Fiorio, M, Cortese, F, & Aglioti, S. M. Deficits of temporal discrimination in dystonia are independent from the spatial distance between the loci of tactile stimulation. Mov Disord. (2002). Mar;, 17(2), 333-8.

[67] Tinazzi, M, Frasson, E, Bertolasi, L, Fiaschi, A, & Aglioti, S. Temporal discrimination of somesthetic stimuli is impaired in dystonic patients. Neuroreport. (1999). May 14;, 10(7), 1547-50.

[68] Artieda, J, Pastor, M. A, Lacruz, F, & Obeso, J. A. Temporal discrimination is abnormal in Parkinson's disease. Brain. (1992). Feb;115 Pt , 1, 199-210.

[69] Tommerdahl, M, Tannan, V, Holden, J. K, & Baranek, G. T. Absence of stimulus-driven synchronization effects on sensory perception in autism: Evidence for local underconnectivity? Behav Brain Funct. (2008).

[70] Haist, F, Adamo, M, Westerfield, M, Courchesne, E, & Townsend, J. The functional neuroanatomy of spatial attention in autism spectrum disorder. Developmental neuropsychology. (2005). , 27(3), 425-58.

[71] Herbert, M. R, Ziegler, D. A, Deutsch, C. K, Brien, O, Lange, L. M, & Bakardjiev, N. A, et al. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain. (2003). May;126(Pt 5):1182-92.

[72] Hollander, E, Anagnostou, E, Chaplin, W, Esposito, K, Haznedar, M. M, Licalzi, E, et al. Striatal volume on magnetic resonance imaging and repetitive behaviors in autism. Biological psychiatry. (2005). Aug 1;, 58(3), 226-32.

[73] Langen, M, Durston, S, Staal, W. G, Palmen, S. J, & Van Engeland, H. Caudate nucleus is enlarged in high-functioning medication-naive subjects with autism. Biological psychiatry. (2007). Aug 1;, 62(3), 262-6.

[74] Rojas, D. C, Peterson, E, Winterrowd, E, Reite, M. L, Rogers, S. J, & Tregellas, J. R. Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. BMC psychiatry. (2006).

[75] Sears, L. L, Vest, C, Mohamed, S, Bailey, J, Ranson, B. J, & Piven, J. An MRI study of the basal ganglia in autism. Progress in neuro-psychopharmacology & biological psychiatry. (1999). May;, 23(4), 613-24.

[76] Voelbel, G. T, Bates, M. E, Buckman, J. F, Pandina, G, & Hendren, R. L. Caudate nucleus volume and cognitive performance: Are they related in childhood psychopathology? Biological psychiatry. (2006). Nov 1;, 60(9), 942-50.

[77] Hardan, A. Y, Girgis, R. R, Adams, J, Gilbert, A. R, Keshavan, M. S, & Minshew, N. J. Abnormal brain size effect on the thalamus in autism. Psychiatry research. (2006). Oct 30;147(2-3):145-51.

[78] Hardan, A. Y, Girgis, R. R, Adams, J, Gilbert, A. R, Melhem, N. M, Keshavan, M. S, et al. Brief Report: Abnormal Association Between the Thalamus and Brain Size in Asperger's Disorder. Journal of autism and developmental disorders. (2008). Feb;, 38(2), 390-4.

[79] Lee, J. E, Bigler, E. D, Alexander, A. L, & Lazar, M. DuBray MB, Chung MK, et al. Diffusion tensor imaging of white matter in the superior temporal gyrus and temporal stem in autism. Neuroscience letters. (2007). Sep 7;, 424(2), 127-32.

[80] Uhlhaas, P. J, & Singer, W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. Neuron. (2006). Oct 5;, 52(1), 155-68.

[81] Just, M. A, Cherkassky, V. L, Keller, T. A, Kana, R. K, & Minshew, N. J. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an

executive function task and corpus callosum morphometry. Cereb Cortex. (2007). Apr;, 17(4), 951-61.

[82] Castelli, F, Frith, C, Happe, F, & Frith, U. Autism, Asperger syndrome and brain mechanisms for the attribution of mental states to animated shapes. Brain. (2002). Aug; 125(Pt 8):1839-49.

[83] Koshino, H, Carpenter, P. A, Minshew, N. J, Cherkassky, V. L, Keller, T. A, & Just, M. A. Functional connectivity in an fMRI working memory task in high-functioning autism. NeuroImage. (2005). Feb 1;, 24(3), 810-21.

[84] Villalobos, M. E, Mizuno, A, Dahl, B. C, Kemmotsu, N, & Muller, R. A. Reduced functional connectivity between and inferior frontal cortex associated with visuomotor performance in autism. NeuroImage. (2005). Apr 15;25(3):916-25., 1

[85] Kana, R. K, Keller, T. A, Cherkassky, V. L, Minshew, N. J, & Just, M. A. Sentence comprehension in autism: thinking in pictures with decreased functional connectivity. Brain. (2006). Sep;129(Pt 9):2484-93.

[86] Cherkassky, V. L, Kana, R. K, Keller, T. A, & Just, M. A. Functional connectivity in a baseline resting-state network in autism. Neuroreport. (2006). Nov 6;, 17(16), 1687-90.

[87] Brown, C, Gruber, T, Boucher, J, Rippon, G, & Brock, J. Gamma abnormalities during perception of illusory figures in autism. Cortex; a journal devoted to the study of the nervous system and behavior. (2005). Jun;, 41(3), 364-76.

[88] Wilson, T. W, Rojas, D. C, Reite, M. L, Teale, P. D, & Rogers, S. J. Children and adolescents with autism exhibit reduced MEG steady-state gamma responses. Biological psychiatry. (2007). Aug 1;, 62(3), 192-7.

[89] Whittington, M. A, Traub, R. D, Kopell, N, Ermentrout, B, & Buhl, E. H. Inhibition-based rhythms: experimental and mathematical observations on network dynamics. Int J Psychophysiol. (2000). Dec 1;, 38(3), 315-36.

[90] Tommerdahl, M, Tannan, V, Zachek, M, Holden, J. K, & Favorov, O. V. Effects of stimulus-driven synchronization on sensory perception. Behav Brain Funct. (2007).

[91] Douglas, R. J, Koch, C, Mahowald, M, Martin, K. A, & Suarez, H. H. Recurrent excitation in neocortical circuits. Science (New York, NY. (1995). Aug 18;, 269(5226), 981-5.

[92] Miller, K. D, Pinto, D. J, & Simons, D. J. Processing in layer 4 of the neocortical circuit: new insights from visual and somatosensory cortex. Curr Opin Neurobiol. (2001). Aug;, 11(4), 488-97.

[93] Bruno, R. M, & Simons, D. J. Feedforward mechanisms of excitatory and inhibitory cortical receptive fields. J Neurosci. (2002). Dec 15;, 22(24), 10966-75.

[94] Alonso, J. M, & Swadlow, H. A. Thalamocortical specificity and the synthesis of sensory cortical receptive fields. Journal of neurophysiology. (2005). Jul;, 94(1), 26-32.

[95] Sun, Q. Q, Huguenard, J. R, & Prince, D. A. Barrel cortex microcircuits: thalamocortical feedforward inhibition in spiny stellate cells is mediated by a small number of fast-spiking interneurons. J Neurosci. (2006). Jan 25;, 26(4), 1219-30.

[96] Cruikshank, S. J, Lewis, T. J, & Connors, B. W. Synaptic basis for intense thalamocortical activation of feedforward inhibitory cells in neocortex. Nature neuroscience. (2007). Apr;, 10(4), 462-8.

[97] Zhang, Z, Zolnoun, D. A, Francisco, E. M, Holden, J. K, Dennis, R. G, & Tommerdahl, M. Altered central sensitization in subgroups of women with vulvodynia. Clin J Pain (2011). Nov-Dec;, 27(9), 755-63.

[98] Zhang, Z, Francisco, E, Holden, J. K, Dennis, R. G, & Tommerdahl, M. Sensory information processing in the Aging population. Frontiers Aging Neurosci. (2011).

[99] Francisco, E, Holden, J, Zhang, Z, Favorov, O, & Tommerdahl, M. Rate dependency of vibrotactile stimulus modulation. Brain Res. (2011). Sep 30;, 1415, 76-83.

[100] Tamas, G, Lorincz, A, Simon, A, & Szabadics, J. Identified sources and targets of slow inhibition in the neocortex. Science (New York, NY. (2003). Mar 21;, 299(5614), 1902-5.

IntechOpen

IntechOpen

IntechOpen