Neural Mechanisms Underlying Temporal Integration, Segmentation, and Input Sequence Representation: Some Implications for the Origin of Learning Disabilities

MICHAEL M. MERZENICH, CHRISTOPH SCHREINER, WILLIAM JENKINS, AND XIAOQIN WANG
W. M. Keck Center for Integrative Neurosciences and Coleman Laboratory
University of California at San Francisco
San Francisco, California 94143-0732

INTRODUCTION

The human brain is a powerful, self-organizing machine that readily generates and manipulates representations of complex input sequences. There has been little study of the physiological mechanisms accounting for several key temporal aspects of perception and behavior, despite their central relevance to our understanding of the neural bases of human cognition and their probable contributions to abnormal operations in special human populations with learning disabilities. Thus, for example, the basic neural mechanisms underlying temporal “integration” and temporal “chunking” or “segmentation” have been incompletely studied. There have been relatively few studies of the representations of temporally sequenced inputs in the brain, and those have been largely limited to piecemeal, single-unit response sampling experiments, or to evoked potential or electroencephalogram (EEG) studies. There have been only a few physiological studies examining the specific conditions under which qualitatively different, temporally simultaneous, and temporally separated stimuli are integrated or are represented categorically, respectively. There has been little specific examination of the nature of distributed neuronal changes accounting for learned, temporally sequenced behaviors underlying the remarkable self-organization of brain function operating throughout a lifetime, but most powerfully in childhood. Finally, there has been little consideration of how what is known about these aspects of dynamic brain function and its ontogeny might account for or relate to the ontogenetic origins of learning disabilities, or to functional brain illnesses.

In this review, we briefly consider our current state of understanding of these important issues of integrative neuroscience from the admittedly limited perspective of our own experiments conducted principally in the somatosensory, auditory, and

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To whom correspondence should be addressed.
motor cortices. We outline specific hypotheses about the neural origins of psycho-
physically measured temporal integration, temporal segmentation, and their plasticity.
We shall consider basic rules underlying behaviorally and cortically manifested
experience-dependent refinement of stimulus representations, and outline some of
the principles underlying dynamic cortical contributions to learning. With this back-
ground, we then state two testable hypotheses about the causes of abnormal temporal
forebrain operations in learning-disabled and other special human populations.

SOME PSYCHOLOGICAL AND
NEUROPSYCHOLOGICAL PREMISES

Psychophysical Measures of Temporal Integration and Segmentation

Psychophysicists have measured temporal integration periods for detection of a
wide variety of inputs, in all sensory systems. In one psychophysical perspective, the
temporal integration period is defined by the minimal duration of a specific, detected
stimulus. In another perspective, the temporal integration period is the time epoch
over which new inputs can add information to a perceived stimulus event. These
basic nervous system processing times have been measured many times in many
specific experiments in vision, hearing, and somatosensation.1-5

One alternative measure that has been used extensively to measure the basic
central nervous system “minimal processing time” or “temporal segmentation time”
is the time separation of a stimulus and a following masker requisite for its detection
or recognition (called the stimulus-to-masker asynchrony, or SOA). In that measure,
a briefly applied stimulus is detected only if it is not backward-masked after a liminal
post-onset time or post-stimulus-offset no-masker period. The fact that a time period
must pass before the arrival of an interfering masker for a signal to be reliably
detected or recognized has been interpreted to manifest a requisite time for forebrain
“processing” of inputs that commonly extends from tens to hundreds of milliseconds
after a brief stimulus.6

A third, related psychophysical strategy for measuring the brain’s processing of
temporal chunks has employed tests of the identification of the temporal order of—or
the identification of separate elements of—two- to many-component input series
(e.g., see P. Tallal10 and B. Moore,11 this volume). In highly trained subjects operating
in audition10,11 or somatosensation,12,13 for example, the spectral identity of se-
quenced input “segments” or “chunks” can be identified if they are about 20 ms or
longer in duration. Much longer stimuli must be applied for correct identification of
stimulus order, as a rule, in untrained individuals. In vision, equivalent estimations
of temporal segmentation times have come from measures of the persistences of brief
stimuli, usually estimated by the use of periodically flashed stimuli.14,15 Similar
stimulus persistence experiments conducted in hearing have measured the temporal
conditions under which periodic stimuli are perceived as continuous,16 or otherwise
modify temporally neighboring percepts.17,18

Some Features of Perceptual Integration Times

1. This base integration period reflects cerebral cortex processing times. It does
not vary with stimulus complexity. On the other hand, stimulus recognition times
differ for tasks of different cognitive complexity. Studies conducted in vision and in
somesthesia indicate that stimulus persistences and backward masking periods are equivalent for spatially simple and spatially complex stimuli.\textsuperscript{19,20} That finding has been interpreted as indicating that the basic temporal smoothing represented by stimulus persistence and perturbed by backward masking occurs relatively early in sensory system processing, in the domain of "primitive" or "preattentive" vision or somesthesia.\textsuperscript{12-22} From a number of arguments considering stimulus feature representation at different sensory system levels, preattentive vision and somesthases are believed to arise from primary sensory cortical fields (e.g., see Julesz;\textsuperscript{22} Karm and Sagi\textsuperscript{24}). At the same time, complex-stimulus recognition requires longer processing times. Prolonged times are attributable in part to the accumulated base integration times that apply to the multiple levels of sensory systems that must be engaged to account for complex image or sound recognition. Thus, for example, the orientation, color, and basic geometrical features of visual "primitives" are recognized separately as integrated features for stimuli flashed in the visual field for a few tens of milliseconds. By contrast, the recognition of transparent motion stimuli believed to require the engagement of a second-level visual cortical field requires several hundreds of milliseconds; while recognition of shape from motion, a task that requires processing of visual information at three or four hierarchical levels, requires many hundreds of milliseconds of processing to emerge.\textsuperscript{25} In this example, direct physiological evidence indicates that the overall time required to make progressively more complicated distinctions about these moving visual stimuli partly reflect requirements for successive input sampling for feature extraction, and reflect the base integration periods of the two or three or four essentially engaged cortical fields. At the same time, when the searching of a complex visual image is required for its recognition,\textsuperscript{21} the time to recognition must reflect the sums of base integration periods of the preattentive visual process that makes up the search.

2. Integration "channels." Within the limits of a base integration or segmentation time, parallel-channel inputs can be added perceptually without substantial interferences. Thus, for example, while color, form, and stereopsis are represented by different neuronal populations that are extracted in parallel with one another, such feature combinations are simultaneously attributable to objects presented to vision within a base time period. Outside of that base time, they are separately perceived and referred.\textsuperscript{26} Integration and time chunking are also achieved by input location-specific channels. Thus, to cite one of many examples, successive binaural clicks with shared spectral properties contribute to an improvement of their localization following a square root of 2 integration rule.\textsuperscript{27} However, they do not affect the localization of clicks that fall spectrally more than one critical band away in frequency, even when those alternate stimuli are presented in a temporally interleaved stimulus sequence.

3. Interruption of integration by novel stimuli. As previously noted, one way to halt integration is by the application of appropriate novel sensory inputs. Backward masks represent one class of interrupting stimuli. In the auditory realm, that interruption has been demonstrated to apply to the ongoing integration process. Thus, for example, the binaural localization of a train of clicks improves continuously following a square root of 2 rule over a roughly 200-250-ms-long integration time period. If integration is interrupted by introducing a distractor—for example, a tone or noise—at an earlier time, the precision in perceptual location is determined by the number of clicks that preceded the distractor.\textsuperscript{28} Such studies (also see Darwin and Ciocca\textsuperscript{29}) indicate that the integration process is begun with the introduction of any new input, but can be reset by appropriate, novel subsequent stimuli.
4. Plasticity of integration time and stimulus onset asynchronies. One of the most surprising features of base perceptual integration and segmentation periods are their apparent plasticity. Thus, for example, stimulus onset asynchronies (SOAs) representing visual primitives in a limited part of the visual field can be reduced to a fraction of their pretraining durations over a 1- to 2-week practice period.\textsuperscript{34, 30} Consistent with their relatively "early" representation in the cortex, those severalfold changes in measured integration periods do not apply to other parts of the visual field or to the representation of other visual primitives, that is, they are specific to the submodal and retinal location "channels" that have been trained. Evidence for location-specific shortening of temporal segmentation times has also been recorded in studies of training-dependent changes in the durations of stimuli whose orientations are correctly identified.\textsuperscript{31} In a related classical study, the durations of displaced letters required for their recognition were found to be subject to significant learning effects.\textsuperscript{32} It might be noted that such perceptual plasticity of temporal integration or chunking phenomena apparently applies to many other aspects of visual acuity, stereopsis, and recognition (e.g., see Gibson;\textsuperscript{33} Bruce and Low;\textsuperscript{34} Poggio et al.;\textsuperscript{35} among many others).

In hearing, durations of detected tones and noises can be shortened 3- to 4-fold by practice.\textsuperscript{36} Detection of the order of sequenced acoustic inputs are subject to similar training effects.\textsuperscript{31} In both behaviors, shorter integration times do not apply to other, untrained frequency domains. In somestheses, we have recently recorded dramatic changes in behaviorally estimated integration times for vibratory stimuli applied to surfaces of the hands of New World owl monkeys\textsuperscript{37} (also see Zwistocki \textit{et al.}\textsuperscript{38}), again consistent with a capacity for severalfold improvement in integration time with practice in this modality. As in the visual case, that improvement is limited to a spatial channel, that is, to the behaviorally engaged skin and a limited surrounding skin domain. Recorded training-dependent improvements in a variety of other tasks involving detection or discrimination of the most fundamental level have also been documented in somestheses and hearing.\textsuperscript{32, 33, 34}

5. Ontogenetic shortening of time chunking. Measures of visual persistence shorten substantially through the course of ontogenetic development.\textsuperscript{42} Similarly, basic measures of integration periods, temporal perturbation effects, and segmentation in audition shorten progressively through infancy and early childhood.\textsuperscript{43-45} The progressive improvements of many other response distinctions have now been tracked in early childhood. Not surprisingly, nearly all have been found to undergo progressive improvement or refinement over tested infancy/early childhood periods (e.g., see Kuhl;\textsuperscript{46} Aslin and Smith;\textsuperscript{47} Chandna\textsuperscript{48}).

Such studies have lead to the general conclusion that subnormal performance in temporal order judgment tasks and in other measures of temporal integration or segmentation times in dysphasic or dyslexic children might reflect a failure in the developmental refinement of temporal processing capabilities. Consistent with that general view, temporal response characteristics for primary visual cortical neurons are substantially degraded in young environmentally deprived animal models, consistent with their having a poor ability to represent rapidly temporally sequenced inputs.\textsuperscript{49} However, the effects of such sensory deprivation are not selective for temporal discrimination effects, but appear to apply to all aspects of sensation and perception that are subject to performance gains with experience (see Beaulieu and Cynader,\textsuperscript{49, 50} for review). Thus, while the overall recorded neurological consequences of severe early deprivation include degradation of temporal integration and segmentation capabilities, they extend nonselectively to include virtually every other measured aspects of fundamental stimulus feature representation.
Abnormal Integration Periods and Temporal Segmentation in “Learning-disabled” Human Populations

Previously cited studies indicate that there is a base short integration period and temporal segmentation for identifying stimulus primitives that are: (a) at least roughly equivalent in all sensory systems; (b) progressively shortens in early child development; (c) can be altered throughout life by a period of experience that engages any part of any sensory system; and (d) can be massively degraded along with other basic sensory capabilities by a prolonged early period of experiential deprivation.

The capacity for behavioral plasticity of integration and segmentation periods is important for consideration here because measures of integration times and temporal chunking are found to be abnormal in a number of clinically important human populations. In general, integration times and stimulus persistence measures are significantly longer than normal in several well-studied populations of learning-impaired individuals including dyslexics. Integration and segmentation times also appear to be abnormal in at least some hyperlexic, autistic, and schizophrenic individuals. An understanding of the origins of cortical integration periods and of possible mechanisms accounting for their plasticity may obviously be important for understanding the origins of these dysfunctional conditions. In this review, we ask: (a) What is the fundamental basis for the nervous system’s generation of detectable and recognizable input time chunks? (b) What controls the time duration of the basic detectable and recognizable input chunk? (c) What mechanisms might underlie the experience-dependent shortening of this basic forebrain process? (d) Could relatively poor temporal segmentation of inputs be learned in ontogenetic brain self-organization? (e) How could a practiced behavioral strategy arising in early childhood plausibly underlie the widespread functional manifestations of abnormal temporal processing recorded in dyslexic and auditory language-disabled individuals? (f) Could a defect in the learning machinery account for the panoply of functional signs that mark a language-disabled individual? (g) What single defect might plausibly explain these signs?

SOME RELEVANT NEUROPHYSIOLOGICAL STUDIES

A Methodological Problem: Adaptive Changes in the Brain Underlying Learning Are Distributed

Why have we not made more progress in understanding how representations of behaviors like reading or speech reception are generated by, and altered in the learning brain? Certainly progress in understanding the neural origins of speech reception have been restrained by the arguments that speech and language reception are not specifically sensory and are uniquely human enterprises, and can therefore not be directly studied in animal models (see Lieberman, this volume). While these issues cannot be reviewed in detail in this context, our perspective is that other mammals have the ability to make equivalent distinctions about complex acoustic stimuli including speech features, if they are trained to do so. There is almost certainly nothing fundamentally unique about speech nor about the basic mechanisms that operate in the cortex that represents it. But while many aspects of its ontogenetic origins can be powerfully studied in animal models, in fact very few have been conducted, and those have been of a limited nature and have primarily involved the study of anesthetized experimental preparations.
A fundamental technical problem that has also limited progress is that these brain operations are distributed widely in the forebrain, in two respects. First, even the simplest of learned behaviors generate changes in several to many of the 60-80 human cortical areas. Second, in a cortical zone engaged by inputs important to learning in any one of these areas, neurons are directly interconnected to thousands or tens of thousands of other neurons, and indirectly to millions or tens or hundreds of millions of others. Therefore, (a) stimuli are represented by distributed neuronal populations; (b) to reconstruct the very complex representations of multiple-component and time-varying signals like speech elements, speech strings, or scanned orthographic word strings, we must "map" engaged cortical areas completely, and in fine detail; and (c) because the effectiveness of specific, complex interconnections between neurons in the cortical mantle and the thalamus are altered by their behavioral engagement, documentation of learning-induced changes must include a reconstruction of this altered internal functional rewiring.

Thus, one important technical challenge faced by cortical physiologists is the task of reconstruction of distributed cortical representations as they change in learning, on the appropriate spatial scale of the dynamic processes of the neocortex. In practice, neuronal responses must be sampled over a narrow time window in relatively fine grain over a relatively large cortical zone in order to reconstruct changes generated by learning involving even the simplest of stimuli—in even a single cortical area. Most of our own experiments have been conducted in the "primary" somatosensory cortex, specifically because the anatomical projection system delivering inputs into this zone is relatively simple and because extrinsic inputs into that zone are anatomically limited in their spreads, permitting easier reconstruction of the distributed representations of relatively simple stimuli. Other studies conducted in the more complexly organized primary auditory and motor cortices confirm and extend basic findings derived in somatosensory cortex.

Cortical Representational Plasticity: Some Implications for The Ontogeny of Human Behavior

Studies conducted over the past decade have revealed that cortical representations of even the simplest features of sensory stimuli including the spatiotemporal representations of sequenced inputs are continuously shaped in detail, by our experiences. Those modifications of the details of sensory representations involve input time-dependent modification of synaptic effectiveness, both for the afferent inputs delivered into a particular cortical field, and for the intrinsic connections within the cortex (see Merzenich et al.,[9-61 for review]. Considered in detail, topographic cortical representations of the ear or skin (and presumably, of the retina) are actually time-based constructs, and can be modified at any point in life by changing the weights and sources of temporally correlated inputs. This capacity for modification by experience is limited by the sources and spreads of inputs delivered into any given cortical location, and by competitive influences from inputs delivered into neighboring cortical zones. Representational remodeling also requires that the input be attended; the rate at which it occurs appears to relate to the strength of the cognitive weighting of its significance or correctness. In any event, the time course of changes relate directly to the time course of learning in any given behavioral paradigm. These adaptive changes in distributed cortical responses and cortical cell assemblies must collectively constitute the cortical contribution to learning and nondeclarative memory.
To illustrate some aspects of the nature of these changes by a single example, consider the representation of the cochlea or of represented sound frequency in a monkey trained to discriminate differences in frequency. In the example illustrated in Figure 1, an adult owl monkey was trained to distinguish frequencies above a 2500-Hz reference frequency in a go/no-go behavioral task. Early in training but after the training was under control, with the animal making few false-positive responses, this monkey could not detect frequency differences of less than about 170 Hz (see Fig. 1A). The animal learned to make progressively finer distinctions as training progressed, so that by the ninety-fifth training session, approximately 20-Hz differences could be detected. At that point, a detailed map reconstruction of the neural representation of sound frequencies within cortical field A1 was recorded. In that reconstruction, the zone of representation of the range of frequencies over which the animal was trained (Fig. 1B) was enlarged severalfold, when compared with control monkeys (Fig. 1C). When we reconstructed sequences of frequency representation within these enlarged zones, very fine shifts in represented frequency were now recorded as a function of cortical location across them (Fig. 1D). In a series of these monkeys, the changes in the territories of representation of the frequencies applied in training were directly correlated with the achieved discriminable differences. Data were consistent with the hypothesis that this finer grained representation resulted in a spatially distinct population being engaged by now-smaller frequency differences.

Note that this experiment reconstructed changes driven within only a single cortical field, the primary auditory cortex, A1. This representation of sound frequency is probably the least mutable of auditory zones, as indicated by its relatively topographically restricted spreads of anatomical inputs, by its relatively predictable representational topography in untrained animals, and by classical conditioning auditory experiments that reveal that far larger and faster changes are induced in several other "secondary" cortical fields in that behavioral context. In any event, behavioral training in even simple forms like this drives representational changes in most if not every cortical field that we study in the given modality. Thus, these changes in A1 almost certainly represent only a fraction of the forebrain area that is driven to change by this behavior.

Similar representational modeling experiments have been conducted in adult monkeys in which always-innervated islands of skin have been moved to new locations across the hand; in both sensory and motor cortical areas in monkeys trained in a pellet retrieval task; in monkeys trained in a tactile frequency discrimination task; in monkeys trained in a skin pressure regulation task; in monkeys performing limb withdrawals signaled by a tactile cue; in monkeys with restricted profound peripheral input deprivation; among many other input manipulations and behaviors (see Merzenich et al. 29). In these various studies (a) substantial cortical representational remodeling was generated in every case; (b) representational changes were related specifically to stimuli, movements, and responses that applied for the behavior; (c) changes were governed by input timing, that is, were generated by differences in the schedules of temporally nearly simultaneous inputs; (d) when inputs were separated with regard to source and time, changes appeared to involve powerful competitive processes that could divide cortical territory between those competitors; and (e) in several specific series in which appropriate measures have been derived, recorded changes in given cortical fields account for measured behavioral gains that result from the training.

Thus, a few minutes of behavior a day for a few days or weeks can generate changes on a major scale in many cortical areas in the somatosensory or auditory or
FIGURE 1. A representative primate brain plasticity experiment. An adult owl monkey was trained to discriminate differences in sound frequency around a 2.5-kHz standard (A). Once the monkey learned the task and performed it with few false positives, psychometric functions (% correct vs. frequency difference) were recorded over 95 subsequent training sessions. The monkey’s discriminative abilities improved progressively with practice, with a roughly 8X finer distinction between frequencies made by the ninety-fifth training session. Neuronal responses in the primary auditory cortical field (A1) were subsequently mapped in detail (B). There, dots represent neuronal sample sites within A1; X’s are sampled sites outside A1. The territory of representation of the trained frequencies (shaded), here understated in a unit “best frequency” map, was found to be greatly enlarged in the trained monkey’s cortex, as compared with a second, controlled frequency range centered around 8 kHz (hatching) or as compared with a normal control (C). As a consequence of this expansion of the territory of representation of the trained frequencies, this specific frequency domain came to be represented in finer grain, as is indicated by a perturbation of the function describing the rate of change of represented frequency as a function of position across the frequency representational dimension of A1 (D). From the study of a series of these trained monkeys, it was concluded that this emergent, finer grained representation likely accounted for the training-induced gains in frequency discrimination. Every simple behavior that we have assessed by this experimental approach has revealed brain plasticity origins of training-induced behavioral gains. (Figure adapted from Recanzone et al.15)

When reflexes are generated in a monkey, a large number of neuronal connections, or motor corticospinal pathways, are involved. This is illustrated in Figure 2A, which shows the distribution of neuronal activity in the primary motor cortex. The top panels of the figure show the distribution of neuronal activity in the primary motor cortex during various motor tasks. The bottom panels show the distribution of neuronal activity during non-motor tasks. The figure clearly demonstrates that the neuronal activity is more widespread during motor tasks than during non-motor tasks. This suggests that the neuronal activity during motor tasks is more complex than that during non-motor tasks. This is consistent with the idea that the neuronal activity during motor tasks is more complex than that during non-motor tasks. This is consistent with the idea that the neuronal activity during motor tasks is more complex than that during non-motor tasks.
motor cortical areas in an adult nervous system. What must be the power of the rapidly growing numbers of repetitions of phonemes or detailed spatial visual scenes or motoric rehearsals that apply to the developing forebrains of young children? By the time they begin school, most children have had hundreds of thousands or millions of repetitions of behaviorally important stimuli that might be expected to generate temporally integrated representational constructs and competitive categorical representational constructs in their nervous systems.

**Integration Time Periods and Distributed Temporal Response Plasticity in the Neocortex**

When repetitive stimuli are delivered into a small sector of the cortical network in a monkey trained to discriminate differences in stimulus rate or frequency, several important changes in the distributed cortical representation of those stimuli occur. Among them, the cortical network generates a progressively more temporally coherent distributed representation of the stimulus elements of the sequence. In the top panels of Figure 2A, the combined responses of all the cortical sites representing stimuli delivered at two different frequencies differing (20 and 26 Hz) for a trained finger location are shown from one monkey experiment. In the bottom panels of Figure 2A, the responses of all of the sites representing stimuli delivered at the same two frequencies for an adjacent, untrained digit site are shown. In the task in which this monkey was trained, the brain's job was to determine whether the second frequency was higher than the first. Not surprisingly, performance was better for the trained than for the untrained site. The crucial difference lay with the distributed response coherence, which was progressively strengthened by the behavioral training. That difference in population coherence was strongly correlated with the behavioral threshold (Figure 2B), and almost certainly accounted for the improvements in these animals' behavioral frequency discrimination abilities with practice. Other possible contributors, like the sharpness of the temporal responses of individual neurons, the cortical area of representation of these stimuli, the tuning of individual neurons, or the response rates of different neurons, do not change very significantly over this learning period, or were not consistently related to discrimination performance gains.

Consider the implications of this simple result for the representation of input sequences. In a naive individual, the distributed responses generated by a novel input are relatively temporally dispersed. They quickly align temporally with training, to generate a progressively more coherent distributed population neuronal response. As a consequence, a salient signal is generated progressively earlier in time; as coherence grows, the representation of this input becomes progressively less confusable with a following stimulus, and can be distinguished from it if it is presented for a progressively shorter segmentation chunk time. Therefore, with training, temporally finer and finer distinctions between successively presented stimuli can be made.

**Formation of Coupled Neuronal Cell Assemblies: Neuronal “Group” Competition**

What changes in the cortex likely account for this change in distributed response coherence? Initial studies indicate that it is at least partly due to an increase in
FIGURE 2. Population poststimulus time histograms for neurons sampled all across a primary somatosensory cortical field representing 20-Hz and 26-Hz stimuli, in a monkey trained to distinguish flutter-vibration frequency difference. The responses in the top panels are the sum of all responses from a densely sampled map of the hand evoked by vibratory stimuli identical to those used in training, and with the stimulation applied to a trained skin site. The responses in the bottom panels in (A) are the sum of all distributed responses with identical stimulation at an untrained site at the corresponding location on an adjacent finger. The monkey's task was to determine whether or not the frequency represented neurally by the distributed responses shown in the right column was higher than (or the same as) the frequency represented in the left column. Extensive analyses reveal that the crucial difference accounting for severalfold performance gains with training was the sharper coherence of representation of individual stimulus events (B). In this series of monkeys, measures of distributed response coherence were correlated with performance gains (B) with a correlation coefficient of 0.98. (Figure redrawn from Recanzone et al.)

1. Intrin. of temporal...
positive coupling of neurons that is a probable result of the strengthening of collateral axonal connections between cortical pyramidal cells. That is, when a limited cortical sector is engaged by new inputs, there are plastic changes in the effectivenesses of thalamic inputs delivered into that zone and changes in effectivenesses of intracortical connections of those pyramidal cells within a local cortical region. When responses from these strongly positively coupled zones are assayed by exciting them with natural stimuli, neurons all across them respond nearly simultaneously to those stimuli. These changes are an instantiation of the classical theorist Donald O. Hebb’s two main hypotheses about the changes in cortical synaptic effectivenesses generated in learning to create “representations” of behavior. His first general rule was that inputs that excite neurons when those cells are depolarized will be strengthened. That is another way of saying that two inputs that generate nearly simultaneous volleys into the network will be mutually strengthened; considered in detail, as is now manifested in many experiments, cortical representations are input coincidence-based. His second general rule was that this time-based remodeling of connections will result in the formation, in the cortical network, of newly connected and temporally coherently engaged “cell assemblies” that will specifically represent each newly practiced input combination. These contemporary plasticity experiments reveal that the creation of emergent or remodeled cell assemblies does occur. But further, they reveal that as the synapses between these new cell assemblies progressively strengthen, distributed responses come to be more strongly locked in time, to progressively more coherently and saliently represent the component temporal chunks of the stimulus(i) that induced the network change.

EVIDENCE FOR INTRINSIC (AND EXTRINSIC) CORTICAL “CLOCKS”

1. Intrinsic oscillators in the cerebral cortex. One of the more complete studies of temporal response characteristics has come from auditory system investigation of the responses to amplitude modulated stimuli, conducted by Schreiner, Langner and colleagues. Among many other findings, they demonstrated that (a) responses at the level of the auditory nerve to amplitude-modulated (AM) stimuli cannot completely account for the modulation-dependent encoding of the pitches of complex spectra; and (b) an orderly spatial representation of the pitches of complex spectra is generated at the level of the principal midbrain auditory nucleus, the central nucleus of the inferior colliculus. At this subcortical level, neurons representing any given band of sound frequency are distributed across neuronal “isofrequency lamina.” Across those functional laminae, predominantly bandpass modulation transfer functions are recorded for the responses of neurons excited by AM stimuli, with neurons at different laminar locations systematically representing “best modulation frequencies” ranging from about 30 Hz to above 1000 Hz. For any given carrier frequency, an orderly representation of best modulation frequency responses spans the normal psychophysical range of periodicity pitch and other complex modulated acoustic signal pitches that apply for that carrier frequency.

Up to and including the thalamic level of the auditory system, some aspects of the spectral and temporal response characteristics of neurons can be roughly described by linear spectral–temporal filter relationships. However, a dramatic transformation occurs within the auditory representations in the cerebral cortex. There, neurons have spectral filtering that is similar to that recorded at subcortical levels, and most neurons still have bandpass modulation transfer functions with well-
defined "best modulation frequencies." However, in the cortex, the best AM frequencies are very low compared with those recorded at subcortical levels. In the primary auditory cortex of cats, for example, they are in the range of about 5 to 25 Hz.\textsuperscript{77-79} In one cortical field in the cat, best modulation frequencies (BMFs) can be higher, ranging up to about 100 Hz.\textsuperscript{80} However, in most "secondary" auditory cortical fields, BMFs are substantially lower, in the range of 2-5 Hz.\textsuperscript{77} Thus, at the level of the auditory cortex, neurons respond strongly to successively presented temporal stimuli only when inputs are "chunked" in time periods (AM cycle lengths) extending from about 50 to 200 ms in cortical field A1, and from about 200 to 500 ms in a series of secondary auditory cortical fields. The shortest of these processing times correspond reasonably well with the minimum durations in which temporal order judgments can be made, and are consistent with the time domains of stimulus persistence or backward masking psychophysical measures recorded in naive human subjects. This A1 temporal chunking is perfectly appropriate for the analysis of inputs at the input rates of speech phonemes. Moreover, the longer best-AM periods of most "secondary" cortical fields blanket the integration time periods appropriate for receiving signals at syllable rates.

During the course of recording these AM response characteristics in auditory cortical fields, Schreiner and Urban\textsuperscript{80} first noted that neurons at many cortical sites had intrinsic oscillations that could be recorded during no-stimulus periods. Moreover, oscillations were often also evoked with application of long unmodulated stimuli, for example, long tonal stimuli. The period of these "intrinsic" oscillations could be determined by autocorrelation. Interestingly, the periods of intrinsic oscillations matched the periods of best-AM stimuli recorded for those same neurons.\textsuperscript{78-81} Moreover, corresponding BMFs were also recorded for neurons that exhibited no demonstrable spontaneous oscillations situated above intrinsically oscillating neurons recorded in the same vertical cortical penetrations. These studies indicate that the time-chunking AM response properties of cortical neurons are influenced by the durations of an intrinsic cortical oscillator.

Interestingly, with application of novel stimuli, the oscillation phase for the evoked neural responses was reset to zero. This may manifest the neurological basis of the resetting of integration time periods by novel acoustic stimuli reported as a major feature of psychoacoustic studies of temporal integration.\textsuperscript{28}

2. Origins of intrinsic oscillations. There are several possible sources of these recorded oscillations—and corresponding temporal segmentation stimulus response characteristics—of cortical neurons. First, physiologists have recently discovered a population of neurons in cortical layer 5 with bursting discharge characteristics.\textsuperscript{82,83} These large pyramidal cells are coupled to neurons in the layers above, so that a mild increase in the excitability of a cortical slice, all neurons in a definable cortical "column" have in-phase, periodic bursting discharges. Such studies indicate the presence of an intrinsic cortical "clock" that might bias or control the modulation transfer characteristics of neurons within its particular cortical column. It might be noted that in these models, a number of coupled, bursting neurons probably comprise the "clock" for a given functional column.

There is equally strong evidence that neurons at most cortical locations respond predominantly transiently to new stimuli, with an early excitatory response followed by a period of strong response suppression. In auditory cortex, the timing of excitatory-inhibitory response cycles roughly matches the cycles of intrinsic oscillations or the best modulation frequency for that site.\textsuperscript{84,85} It may be that the excitatory modulation contributed by the bursting neurons of layer 5 are strong enough to account for this excitatory-inhibitory cycle, but more likely, intrinsic processes involving...
involving sequential excitation-then-inhibition are adapted by mechanisms of plasticity to match—and therefore amplify—the base period contributed by the intrinsic clock.

Other investigators have argued that modulation transfer response characteristics might reflect the operation of intrinsic vertical cortical circuitry. For example, responses in granular and supragranular layers might reverberate through infragranular layers. This and other reverberatory circuitry is certainly in place, and some features of response time in regard to cortical layers recorded in cortical slices and in vivo preparations are consistent with this vertical, interlayer cortical reverberation. Again, such circuits may be selected in learning to sharpen temporal representations, and/or may well play a role in amplifying or modulating the base period of an intrinsic cortical clock.

A fourth notion, argued about since the discovery of oscillations of cortical responses in EEG signals many decades ago, is that cortical response oscillations derive from extracortical sources. In classical studies, investigators demonstrated, for example, that cortex could be dominated by oscillatory responses arising in the thalamus during sleep spindle periods. At the same time, it was demonstrated nearly 40 years ago that oscillations can also be recorded in undercut cortex that has no thalamic inputs. These arguments have been resurrected in a modern context by evidence that oscillations in the theta frequency range (25–50 Hz) come from extracortical sources, for example, from the thalamus or hippocampus. On the other hand, since the cortex has bursting neurons that can impose temporal chunking response characteristics on the cortical columns they connect with, it has been argued that extrinsic oscillatory inputs may modulate already-present cortical oscillators. This very important issue remains to be clarified.

*Are the Base Frequencies of Intrinsic (and Extrinsic) Cortical "Clocks" Plastic?*

We have already described one form of temporal sharpening that may relate to the experience-dependent shortening of "temporal chunk" times observed psycho-physically. Thus, practice with sequenced inputs results in the generation of more coherent distributed representations of individual stimulus events, which increases their salience and which shortens the time the system requires to identify them, and to separate them from a following masker or distractor or second stimulus. That facet of cortical plasticity may alone account for the plasticity of temporal integration periods, SOAs, pulsation threshold, temporal order judgment, et alia. However, the basic temporal segmentation time represented by intrinsic bursting neurons is probably also plastic. Thus, for example, Connors and colleagues have shown that a very weak depolarization of these neurons in cortical slices results in significant increases in their burst rates, that is, in a significant shortening of their base clock periods. Changes in input effectiveness in a cortical column that is differentially engaged by taking up a new behavior would be expected to generate such changes. This important hypothesis is now being tested in animal models, in studies that are ongoing in our laboratories.

Are these two interesting temporal phenomena—that is, best modulation frequency response characteristics probably derived from an intrinsic "clock" and representation of input salience by the distributed response coherence of neurons in the engaged cortical sector—directly linked? In fact, bursting neurons in layer 5 are also coupled by pyramidal cell collaterals, and that coupling is presumably strength-
en by any behaviorally important input that selectively engages them. That should result in a positive change in their response coherence, and in a progressive increase in the numbers of leading neurons controlling a given behaviorally exercised column. A second consequence would be that when the behaviorally trained inputs drive the system, these neurons would be more strongly depolarized because of these more coherent connections, which should result in a shortening of their oscillation cycle times. Thus, the same set of plastic changes that generate more coherent—and hence, more easily temporally distinguished—components of temporal sequences hypothetically should also generate changes in the basic “clock” times contributed by intrinsic cortical oscillators. The possible linking of these effects will be resolved in experiments that are now being conducted in our laboratories.

**Possible Relationships Between BMF/Intrinsic Oscillation Response Characteristics and Response Bandwidths**

In linear systems, there is a direct relationship between input bandwidths and temporal response characteristics. As noted earlier, that condition is roughly maintained in the mammalian auditory system up to the level of the medial geniculate body. In the cortex, there is a highly nonlinear treatment of inputs that are modulated in time. However, it is reasonable to hypothesize that the much slower modulation rates of cortical neurons will still be directly related to spatial bandwidth. In general, the wider the scope of inputs, the more difficult it will be for neurons to generate a strongly coherent representation of incident temporal events, because there should be correspondingly more temporal input dispersion. We have just begun to examine the relationship between input bandwidths and clock periods in cortical field A1. In initial auditory studies, they appear to be related.

**Temporal Dispersion of Outputs from First-order Cortical Processing: Implications for Higher Order Processing**

Note that the cortical sector representing any given sound frequency in a cortical field like A1 has an orderly representation of neurons with different bandwidths, and a corresponding range of neurons with different best modulation frequencies. That is to say, when a new input is received by A1, its “clocks” are all started roughly in unison; however, the next point at which inputs will be effective will depend upon the unit clock time for each cortical locus, with those times varying in untrained cortex from about 40 ms to about 200 ms. The cortex can provide a strong output representing a second transient input any time over that time period, and it will be fully engaged in representing a second event beyond that time. This constitutes a basis for distributing the representation of a second input in cortical space in a form that permits a selection of inputs for specific temporally sequenced inputs by neurons in higher order cortical areas that have longer chunk times, for example, permitting integration at syllable rates.

Note that this does not mean that cortical neurons cannot selectively represent spectral features that occur in sequence at rates higher than 20–25 events/s. In fact, neurons across the isofrequency representational axis of A1 are selective for spectral details like FM sweeps, FM sweep directions, broader spectrum versus narrow—spectrum stimuli, et alia, and with training, the cortex can encode and represent them at a later time. The visual sensory epithelium, frequency—levels of the conferring a varying input

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them at a level adequate to account for human phonetic discrimination abilities. There is evidence in humans that even the pitches of complex spectra might be represented spatially (not temporally) within the primary auditory cortical field.67

The visual cortex also creates an iterative representation of each point on the sensory epithelium in its orderly representation of stimulus bandwidth or “spatial frequency” within primary visual cortex “hypercolumns.” This infers that the higher levels of the visual system also treat inputs across a range of “chunk times,” again conferring a capacity to create highly selective representations of specific time-varying input sequences.

CONCLUSIONS: HYPOTHESES

From these observations, we proffer two basic testable hypotheses about the origins of speech and language disabilities including dyslexia of central nervous system origin that are marked by longer than normal temporal integration and segmentation period lengths that apply to inputs in all three principal sensory modalities and to the production of fine movements.

Hypothesis 1: “Deficiencies in Temporal Processing Are Learned. Could dyslexia and developmental dysphasia arise because some infants adopt more global hearing or looking strategies? Many aspects of eye movement behavior as well as studies of abnormal peripheral masking effects and improved reading with peripheral masking are consistent with the hypothesis that these special children operate in vision with a wider-than-normal field of attention. A consistently wider field of view should result in a degraded ability of the system to generate temporally sharpened representations from always-wide-bandwidth—and hence, temporally noisy—inputs. Heavy experience with such inputs might be expected to alter the base oscillation periods of visual cortical fields downward, because (a) those base periods are plausibly linked to input bandwidth and/or (b) as a rule, the strength of depolarization of clock neurons would depend upon the strengths of their own intrinsic inputs, and the more temporally dispersed those inputs, the lower their states of depolarization, and therefore the lower their base clock rates.

Note that very early visual practice with a wider field of view does not necessarily represent a “deficient” or “negative” or “dysfunctional” behavior. To the contrary, it would probably represent a practice strategy that, from the visual system’s point of view, presents advantages for the rapid processing of relatively complex, spatially distributed inputs, especially for a very young brain. Such an alternative learning strategy might be expected to arise with higher probability in preterm infants because their oculomotor and focus control is more primitively developed when visual behavior is initiated.68

Once a “bad” looking (or listening) strategy is in place, by this hypothetical scenario, visual scene representation at every cognitive level as well as eye movement representations would be powerfully reinforced by the many tens or hundreds of thousands or millions of input repetitions. When reading was initiated, it would be initiated in a brain that had been powerfully trained and reinforced in countless operations to scan visually with a wide field of view. When the reading lesson stopped, the visual operations of the nervous system continue to work to reinforce and to sustain inappropriate forms of representation. In this scenario, reading practice that did not control for the field of view would only work to further reinforce the enduring problem, and to forestall its ultimate resolution. For example, vergence
control for small visual targets would not be expected to have developed normally, because this behavior would have been unpracticed. On the other hand, vergence control for larger visual targets would develop more normally. In a childhood reading lesson, thousands of repetitions involving vergence with larger visual targets could occur, further strengthening the dominance of the burned-in strategy. No matter how intensive, training from this and other specific learning perspectives could have substantially negative—not positive—consequences. Moreover, away from the reading class, a child’s other lessons, addressed without visual control, could further reinforce “bad” looking, and coupled with the rest of the day’s rich visual operations frustrate the small neurological consequences of a reading lesson. In many children, lack of success in reading would result in an attenuation of possibly corrective practice in any event.

How might an “error” in brain self-organization account for a general error in processing of rapidly sequenced inputs that also applies to auditory, somatosensory, and motor operations? Recent studies have revealed that activity is normally temporally coupled over long distances in the cerebral cortex, between modalities, and to some extent between hemispheres. This cross-modal and cross-region coupling is manifested by recording in-phase oscillations in brain activity, for example, across the somatosensory and motor cortex in a monkey performing a tactually guided motor task, or between area 17 and “higher” visual cortical areas. It is probable, then, that a basic deficiency in timing input sequence would reflect the operations of the weakest cortical link in this chain of temporally coordinated processes: All must track the slowest participant in their temporally coupled representation.

Could the timing problem first originate with an “inappropriate listening” or haptic strategy? Hearing, like vision, could very well be the usual source of the inappropriate field of focus, and could well impose its “bad” timing on visual operations. For reasons that are beyond the scope of this brief review, the somatosensory system is less likely to be the original source of time chunking deficiencies.

If these special temporal processing-based learning disabilities arise by a learning scenario, on the basis of what we understand about brain plasticity and learning ontogeny, can they be reversed? That question cannot be answered with clarity, nor can there be any certainty that all cases are alike in this respect. However, the brain of a child and even an adult is capable of remarkable representational remodeling. If a learning-origins hypothesis applies, then what must be overcome in retraining is the massive accumulated weight of experience derived from all earlier life, as well as the potentially daily confounding inputs that occur away from the reading class. Reversal of this situation could be painstakingly slow, but is clearly possible. Several potential manipulative strategies for greatly accelerating the rates of change in learning systems are under investigation. They might be expected to ultimately greatly facilitate the training process in learning-disabled children.

**HYPOTHESIS 2: There Is a Locally or Globally Expressed Physical Defect in the Learning Machine.** We have earlier noted that the temporal integration periods and segment lengths shorten through development, and can be shortened throughout life by practice. The creation of more coherent representations of stimuli in learning and the probable plasticity of basic cortical “clock” times in child development and throughout life are dependent upon the operation of basic mechanisms of synapse strengthening. The list of the molecular elements of the forebrain machinery underlying the modification of synaptic effectiveness in learning is a very long one; a defect in any one of at least several hundred proteins, for example, could potentially result in some attenuation of rates of learning, and hence, in prolonged temporal integration of normal i (s) reading stantial im defect mus processing movement deletion of process car other behav almost sible that temporal p expectation

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integration and segmentation times. It has been established that dyslexic children are
of normal intelligence, when evaluated in nonreading tests. That would suggest that
(a) reading challenges a mildly deficient system in a way that does not have sub-
stantial impacts on other aspects of associative learning; and (b) that the physical
defect must apply selectively to plastic changes that control aspects of the temporal
processing of inputs, or perhaps to strategies for looking or for controlling eye
movements (see before). A recent gene-deletion study in mice has argued that the
deletion of one key protein kinase believed to be critical for a fundamental learning
process can result in a deficit in some aspects of learning in some brain regions, while
other behaviors and other brain regions may not be significantly affected. Given
the almost innumerable possible consequences of genetic mutation, it is very pos-
sible that specific genetic defects could produce functional deficits selective for
temporal processing in these learning systems. At the same time, a far more common
expectation would be the appearance of a general learning deficiency.

With a small established defect, it might be difficult to reduce temporal chunk
times down to their usual minima. For example, a defect might result in a dispersion
temporal inputs that limits the achievable levels of response coherence or “clock”
times. It might limit the achievable changes in depolarization, and hence, the possible
reductions in base “clock” times because of a limitation in the power of presynaptic
or postsynaptic contributors to long-term potentiation. Moreover, (a) when the self-
organizing mechanisms of the brain operate behaviorally with the defect in place,
suboptimal experiential driving of the system would further reinforce and distribute
its prolonged minimum temporal chunking, à la the scenario outlined earlier; and (b)
lack of effective practice in a learning-disabled child ensures that these specific
aspects of learning usually remain underexercised, an experiential fact that could be
expected to contribute to the stabilization of deficient temporal processing. A
defect in the learning machine would not necessarily have to be expressed globally;
a disabling defect applying principally to vision or to hearing could presumably
impose its timing limitations on other sensory systems.

Concluding Remarks

Functional limitations imposed by “inappropriate” learning strategies adopted by
our self-organizing nervous systems early in life must occur—indeed, must account
for many aspects of the rich variety of human abilities that stamp us all as individual.
We are now entering an era in experimental neuroscience in which we are beginning
to understand how experiences generate changes in the nervous system that shape
our language, our visual world, our coordinated movements, our cognition. A vision
of how our ontogenetic, day-by-day experiences might account for our individual
limitations and for the remarkable variability in human performance abilities is
gradually emerging from these studies.

In parallel, neuroscientists are defining the organizational details and mecha-
nisms of the learning machinery of the brain. The complex, neuronal circuit, cellular,
and molecular processes that account for acquisition of complex “basic” skills like
speech reception and reading are subject to many possible inherited deficiencies.
Genetic defects partially disabling the learning machinery must occur. We are now
entering an era in which the consequences of such mutations and gene dropouts can
be assessed.

Both of these growing neuroscience subdisciplines must be tasked with determin-
ing whether and how the adoption of specific early learning strategies and/or how
specific genetic defects might selectively alter the neural representations of temporal integration and segmentation. Our challenge is to press consideration of these two origins hypotheses along with their alternatives (e.g., Livingstone and Galaburda's), from the special perspective of the psychophysical and operational capabilities of these very extraordinary human populations.

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“Developmental ability, which is logical diagnosis and emotion (cognitive development) does not differ from the means of diagnosis based upon observation. Neurologically, the primary aspects of dyslexia are cognitive output inefficiency and persistent cognitive symptomatology, lexia” when language development is at risk. The linguistic conditions in undiagnosed cases.

Yet the diagnosis of dyslexia is particularly important because of the potential for effective interventions. Speech disorders (sp. ADHD, writing, or organ mechanisms) are well-adapted for patients with these deficits.

Cognitive