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Review article

The Role of Dynamic Columns in Explaining Gamma-band Synchronization and NMDA Receptors in Cognitive Functions

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Abstract: The role of gamma-band synchronization and NMDA receptors in cognitive functions and neuropsychiatric disorders has received increased attention over the past two decades, with significant controversy about their roles. The role of the cortical column as a basic unit in cortical processing has also been debated. The current paper presents the theoretical argument that the dynamically formed column is the binary unit (bit) involved in all cortical processing and memory, and that gamma-band synchronization is required for columnar formation. Moreover, the role of NMDA receptors is explained as allowing the consolidation of synchronized boundary minicolumns that serve as the bit, as well as strengthening the connections among the circuit of columns that are involved with any given memory. Following a discussion of the microcircuitry that may be involved, there is a brief discussion on how the serious neuropsychiatric disorders of schizophrenia, autism, and Alzheimer's disease can be conceptualized as disorders of disrupted column formation. The arguments presented provide a theoretical basis for future research to determine the validity of this novel view.

Keywords: cortical column; gamma oscillations; synchronization; NMDA receptors; cognitive functions; memory; schizophrenia; autism; Alzheimer's disease

Abbreviations

AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Bit	binary unit
BOLD	blood oxygenation level-dependent
CaMKII	calcium-calmodulin kinase II-alpha
EGO	early gamma oscillation
FS	fast spiking
fMRI	functional magnetic resonance imaging
GABA	gamma-aminobutyric acid

IPSCs	inhibitory postsynaptic currents
ING	interneuron gamma
LFP	local field potential
MC	Matinotti cell
NGC	neurogliaform cell
NMDAR	N-methyl-D-aspartate receptor
PV	parvalbumin-expressing
PC	pyramidal cell
PING	pyramidal interneuron gamma
RS	regular spiking
SBC	single-bouquet cells
SOM	somatostatin-expressing
SRR	synaptic reentry reinforcement
VIP	vasoactive intestinal polypeptide-expressing

1. Introduction

Since gamma-band synchronization was observed in the primary visual cortex neurons of cats in response to moving light bars in 1989 [1], there has been extensive research into the role that such synchronization plays in neural processing. Not only has gamma synchronization been reported to occur in a functional column, it is also observed that neurons in spatially separate columns can synchronize their oscillatory responses [1–3]. These findings led to the hypothesis that synchronization of oscillatory responses may have a general function in cortical processing as a powerful mechanism to establish assemblies of cells with coherent phase and frequency oscillations [1].

Singer [4] reviewed the neural synchrony literature and hypothesized that neural networks encode information about the association of responses using both conjunction-specific neurons and by temporal coordination of distributed responses. By adjusting the temporal relations among distributed neuron discharges, represented information can be selected with high temporal resolution for further joint processing. This mechanism was seen as a way to establish temporary bonds in a highly dynamic and flexible way. Fries [5] subsequently expanded upon this "binding-by-synchronization" hypothesis by suggesting an interaction between gamma-band synchronized networks and the influence of low-frequency rhythm. Within this framework, there is selection of only one segment of input at a given moment, with the remaining input being sampled segmentally at a low frequency rhythm.

There have been criticisms of the binding-by-synchrony hypothesis. Ray and Maunsell [6] evaluated the effect of stimulus contrast on gamma frequency in the V1 cortex of macaques, concluding gamma rhythm was not likely involved with binding or communication. Similar conclusions were reached by examining gamma power and peak frequency or strength of spiking activity in macaque V1 [7]. Moreover, Burns et al. [8] found no evidence that V1 local field potential (LFP) contains any clock-like gamma-band signals. Reviewing these and other findings, Merker [9] concluded that there are no compelling reasons to accept any functional role for gamma-band synchrony beyond its more generic function at the level of infrastructural neural control. However, the exact neuronal infrastructure that may be controlled has not been elaborated. If the infrastructure

is identified, it seems reasonable that there can be an alternative view of the binding-by-synchrony hypothesis.

Some studies have noted that the synchrony occurs within cortical columns [3,10], but there has not been a detailed discussion of the manner in which cortical columns may be involved. Mountcastle [11] was the first to theorize that the vertical grouping of cells across all cellular layers in the somatosensory cortex is an elementary unit. He named this unit a "column." He later proposed that the column is formed by many "minicolumns" via horizontal connections [12]. Despite its endurance as a fundamental principle of cortical organization, Horton and Adams [13] reviewed 50 years of research on the cortical column and concluded that extensive research has failed to provide a comprehensive explanation of exactly how this functional unit is involved in information processing and memory storage. They noted the variability of definitions used to define columns, with a lack of support in how minicolumns and columns are interconnected. They cited studies that failed to demonstrate clear boundaries of minicolumns and that there was no consensus on the number of minicolumns present in a functional column. They discussed that it is hard to reconcile species variations in columnar structure with the functional importance of columns. In conclusion, they suggested the column might have no actual function.

If cortical columns do indeed have a function within the architecture of the cortex, the challenge for any theory is to explain these conflicting findings. Moss [14] theorized that the column is the binary unit (i.e., bit) involved in all cortical cognitive processing and memory storage. This theory provides one explanation for some of the conflicting results in the literature. For example, the theory provides an explanation of the relationship between columns and minicolumns by suggesting that columns overlap so that they share a number of common minicolumns. In an updated review and revision of the theory, the relationship of columns to gamma-band synchrony is explained in a manner consistent with much of the literature [15]. This columnar model (the Dimensional Systems Model) has been discussed in detail in relation to cortical processing patterns [14,15] in addition to its applications to psychotherapy [16]. However, there have been only brief discussions of the involvement of columnar microcircuitry and synchronization to this point in time [14,15,17]. The current article extends this theory by incorporating a more detailed analysis of the mechanisms that can lead to dynamic column formation based on gamma frequency oscillations. The first section briefly discusses aspects of the Dimensional Systems Model (DSM). Next, the theorized mechanisms involved in dynamic column formation are presented followed by a discussion on how synchronization applies to cognitive functioning based on the columnar model. Then the microcircuitry underlying this synchronization is discussed, and finally, implications for cognitive dysfunction in disorders such as schizophrenia, autism, and Alzheimer's disease are presented.

Overview of the dimensional systems model

Although the model emphasizes cortical mechanisms involved in learning and memory, it necessarily includes the manner in which sensory input and subcortical functions interact with these cortical mechanisms. All nervous system functions are considered to exist for the purposes of survival. The manner in which received information is processed and encoded is viewed as being directed toward an accurate representation of all salient aspects of external and internal stimuli. There is a corresponding mechanism to make use of this encoded representation to allow specific response patterns to be evoked based on specific characteristics of the representation. Given the need for accurate details in a reliable fashion, a discrete system of coding tied to processing and response appears most logical. If that assumption is accurate, then probabilistic, complex, and continuous

signaling patterns of cortical coding would not be expected to evolve based on the simple assumption that such complex processing would be a major disadvantage for species' survival. This assumption does not deny the fact that individual neurons encode information in variable rate spike trains. However, the argument is that the representation of groups of neurons organized in a columnar fashion is best conceived of as implementing a single discrete piece of information (i.e., a bit).

Moss [14] provided the first detailed description of the DSM, followed by a later update with revisions [15]. The influence of Luria [18] is obvious in the relation to the view that higher mental functions involve the whole brain, not just the cerebral cortex. An understanding of cortical activity necessarily involves the reciprocal interactions with numerous subcortical areas. However, understanding the manner in which the cortex processes and stores information is crucial.

To assist in understanding cortical processing, two points will be helpful. First, everything works in circuits. Second, the components in the circuit determine what functions occur. For example, a simple electrical circuit involves a power supply, a component or device (e.g., light bulb, buzzer), and the wires connecting these. Usually there is a switch that serves to activate and deactivate the circuit. If a light bulb is in the circuit, it glows when the switch is in the on position. If there is a separate circuit with a buzzer, the buzzer does not activate when the light bulb circuit's switch is on because it is not connected to that switch. If both the buzzer and light bulb are connected in series in the same circuit, there is both light and sound when the circuit is activated. Alternately, the light and buzzer can be in two separate circuits but connect to a common switch that activates both circuits simultaneously, thus being in parallel. When the common switch is activated, both the light and the buzzer activate. The distinction between components being in series versus parallel will be used to explain multisensory and association memories respectfully. Therefore, it is easy to see that if components or devices are not connected to a given circuit then there is no expectation they will activate.

The concept of disconnection syndromes is one familiar to neuropsychologists [19]. In such a case, if the neural connection, or wiring, is severed between two brain areas, then functions that depend on those areas working in concert are disrupted. Within the context of the DSM, circuits of columns that do not interconnect have no means to access one another even though each circuit may have the capability of processing incoming information and initiating a response.

The basis of the DSM is that the cortical information binary unit (bit) is the cortical column. This simply means that each cortical column represents specific and discrete information. Briefly, a column is comprised of several hundred minicolumns each of which may contain approximately 100 to 200 neurons [20]. The diameter may vary from approximately 0.4 to 1.0 mm, depending upon the cortical location and species. Because information stored in the cortex is important to preserve, the large size fits well with the need for structural stability and resistance to damage of an information unit involved in processing. However, an obvious criticism is that the information capacity of the cortex is enormous and the surface area does not appear sufficient for the required number of such large columns. To explain how this is possible, Moss [14] suggested that columns overlap such that some minicolumns are shared. Moss et al. [15] added the propositions that only the outer minicolumns comprised the actual columnar bit and that minicolumns may also overlap.

In relation to the DSM, five systems are identified. The sensory input system focuses primarily on tactile, auditory, and visual input as being the most influential in higher functions and related to the manner by which processing occurs in specific cortical areas. The arousal system involves the power supply to the cortex necessary for processing and memory storage which can be selectively enhanced based upon ongoing biological needs and emotions. The attention–memory system involves the structures and mechanisms by which incoming sensory information is selected and

subsequently stored in memory at the cortical level. The cortical system involves the means by which the columns interact to provide processing, analyses, and responses. Finally, the motor system describes the output level of the system by which environmental manipulations occur.

Moss et al. [15] provided a physiological definition of memory which involves the strengthening of synaptic connections in any given circuit of cortical columns that are used in information processing. The strengthening occurs due to ongoing reactivation of all the columns in the circuit. The ongoing activity initially impacts neurochemical factors (e.g., ionic concentrations, neurotransmitter stores), followed by gradual synaptic structural growth (i.e., increased axonal boutons and dendritic spines). Forgetting is the result of weakened synaptic connections which means the downstream columns in the circuit fail to activate. In this case, the column's activation by one or more other columns fails to be maintained. However, with structural changes, such as axonal sprouting and increased dendritic spines between neurons of columns, then the likelihood of "forgetting" is greatly reduced because the connections are resistant to disruption and damage.

There are several important aspects tied to this definition of memory. First, all memory tied to higher functions occurs at the cortical level and all memory involves the same mechanisms. The perceived quality of a memory is a function of the information represented by the columns involved, in the same manner that the previously discussed light bulb and buzzer determine the output of simple electrical circuits. Thus, columns in the temporal cortex that code for spoken words are perceived as spoken words, while those in the parietal lobe that code for body sensations are perceived as sensations when activated. This view of memory is consistent with the idea of contextual reinstatement for memory retrieval [21] that has been supported by a number of neuroimaging studies showing cortical reinstatement of encoding activation during retrieval [e.g., 22,23]. In the case that both sound and touch are simultaneously activated, the convergence zone in the parieto-temporal area would have a common column that codes for the multisensory experience and memory (i.e., in "series"). If the processing of stimulus information involves multiple circuits in which the direction of processing does not converge, then columns in the medial temporal lobe become the common projection point for all those circuits (i.e., in "parallel").

Similarly, explicit (i.e., declarative) memory and implicit memory are both circuits of columns, with the qualitative distinction being whether the "interpreter" [24] has direct access to the memory. It has been proposed that for the majority of humans the left (as opposed to the right) lateral ventral frontal area (i.e., frontal operculum) is the theorized location of self-talk, or internal verbal dialogue, and is what defines declarative memory (i.e., being able to verbally explain what is being remembered) [14,25].

Subcortical enhancement of memory occurs as a function of the activation of the cortical circuit which in turn strengthens the synaptic connections of the involved columns. Increased general arousal via the reticular activating system and increased selective arousal, such as occurs with amygdala involvement, increase cortical arousal which strengthens the synaptic connections among the columns involved in processing and memory of related stimuli. The hippocampus serves to maintain a hippocampal–thalamus–cortical–hippocampal circuit with the goal being strengthening of the synaptic connection among columns.

In sensory cortex, input leads to the activation of columns in the primary receiving areas. The downstream location where efferent activity from the activated upstream (called "lower-order" or "less organized") columns cross becomes entrained as a new higher-order column. Additionally, it was posited that for each posterior lobe receptive column that forms, there is a corresponding action column that forms in the frontal lobe [15,16]. In contrast to the binding-by-synchronization

hypothesis, the column theory views gamma-band synchronization as a necessary mechanism allowing the formation of these higher-order columns that are the actual discrete information units. Consistent with the conclusions of Merker [9], the generic function is related to infrastructural neural control in relation to column formation and duration of feed-forward signaling.

Because environmental factors vary, there must be a mechanism to allow plasticity in determining the salient stimuli at the cortical level. Thus, stimulus input received cortically programs the primary receiving areas. As will be discussed later, gamma-band synchronization provides a mechanism for programming. In addition to discrete stimulus coding (e.g., sound frequency activating tonotopic columns), there are frequently repeated combinations (e.g., phonemes and syllables in spoken language) of those discrete stimuli that are salient as well.

The nature of sensory stimuli appears to have determined the processing mode of cortical regions. Sound is a sequential pressure sense leading to a sequential processing mode in the temporal lobes. Somatosensory input involves simultaneous (i.e., multiple locations) pressure stimulation leading to a simultaneous processing mode in the parietal lobes. Vision involves both sequential and simultaneous processing, involving a ventral stream if sequential aspects are most relevant versus a dorsal stream if simultaneous aspects are involved.

Moss et al. [15] suggested several cortical dimensions in relation to the information being coded in a particular column that are summarized in Table 1. Another aspect of the model is that for each column involved with receptive processing in the posterior lobes, there needs to be a corresponding action column to allow the information to be used by the organism. In reference to the location of columns, there is an expected topographical arrangement. For example, the ventral columns involved with sequential information connect to ventral action columns, while simultaneous dorsal receptive columns connect to dorsal action columns. Primary somatosensory columns connect to primary motor columns, while secondary somatosensory columns connect to premotor frontal columns. The receptive auditory phoneme and syllabic columns connect to the phoneme and syllabic action (i.e., motor planning) columns involved with speech production in lateral cortex. Visual receptive columns connect to action columns in the area of the frontal eye field. Tasks that require both simultaneous and sequential processing, such as visual tracking of an object, involve areas intermediate to the dorsal and ventral streams.

As indicated, cortical processing and memory involve circuits of columns. Therefore, all factors leading to enhanced memory formation have the common denominator of increasing the strength of synapses among the columns of that particular memory. Increased arousal, whether tied to emotions, biological needs, or both, would lead to enhanced memory formation via increased synaptic activity and therefore strengthening among columns. Similarly, enhanced memory consolidation tied to sleep is the result of increased activity and synaptic strengthening in the columnar circuit. Reciprocal connections of individual columns to one another and to the thalamus allow reentrant signaling. In relation to association memories involving parallel circuits of columns in distant cortical areas, the hippocampus serves a starter and pacemaker role in a cortical-hippocampal-thalamic-cortical network that has its primary role being the strengthening of synapses in the columnar circuit. Therefore, memory formation is the same throughout the cortex regardless of type of memory. The perceived quality of a memory is a function of the information represented by the columns involved.

The original Dimensional Systems Model articles provide a more detailed discussion of other aspects of the model and its use in psychotherapy [14,15]. The foregoing description provides an illustration of the role of columns in the model in order to provide a basis for the following discussion about the circuitry that comprises columns and provides a mechanism for the necessary columnar circuits to form.

Table 1. Dimensions of Cortical Column Organization in the Dimensional Systems Model

Dimension Name	Description of Dimension
Internal-external	The medial cortical columns code stimulus information that is internal and self-referential while the lateral cortex codes for external stimuli. Intermediate or transitional zones code for combinations of both.
Proximal-distal	In relation to proximal versus distal to the body stimulus coding, the central sulcus is considered the most proximal cortical location. The post-central sulcus parietal cortical area would code for somatosensory (i.e., body sensation) stimuli. Both vision (occipital lobe) and audition (temporal lobe) involve distal sensory information. The pre-central sulcus primary motor strip involves the body directly while anterior prefrontal processing involves information manipulation largely independent of the body.
Simultaneous-sequential	Ventral cortex processes in a sequential manner and dorsal cortex in a simultaneous manner, with intermediate areas using both modes of processing
Reception-action	The parietal, temporal, and occipital lobes contain all receptive, or sensory, information while the frontal lobes code for all action-related information.
Unorganized-organized	Receptive information progresses from less-organized, or lower-order, information to more-organized, or higher-order, information (i.e., coding) as the stream moves away from the primary sensory receiving areas (i.e., bottom-up processing). On the other hand, the frontal action columns progress in a rostral to caudal more-organized, or higher-order information to less-organized, or lower order information (i.e., decoding) as the stream goes toward the premotor and primary motor areas. The frontal action columns' control of posterior lobe receptive columns is also present (i.e., top-down processing).
Analytical-Global	Each cortical hemisphere acts as a separate, albeit interconnected, processing unit which means that each of the aforementioned dimensions is contained within each hemisphere. However, there are fewer columns from the time of sensory input to the response level in the right hemisphere. This means that the right cortex can process information faster, but with fewer details (i.e., global processing). The greater number of interconnected columns in the left hemisphere allows more detailed processing and memory storage (i.e., analytical processing)

Column microcircuitry design

There are two key ideas in the model that are consistent with the organization of the cortex while also helping to resolve apparent conflicting findings regarding the role of cortical columns and the function of gamma oscillations. First, the dynamic organization of columns from minicolumns is consistent with recent findings and helps to explain why others [13] have concluded that there is no function for columns. Such a design means that there would not be structural indications of a static column; instead, there should be a design that allows the dynamic formation of the column. The second idea is that the role of gamma oscillations is related to the gamma-aminobutyric acid (GABA) inhibition necessary for the formation of dynamically organized columns and limiting the duration of feed-forward signaling from a column.

In terms of dynamically-formed columns, there have to be mechanisms that allow for stability of the dynamic columns, and several relevant findings support this idea. These mechanisms have to rely on the local microcircuitry of minicolumns. Notably, there are several studies that suggest the formation of columns occurs with the involvement of only a few pyramidal cells PCs. Although this has been interpreted as "sparse coding" by some authors [26], the current proposal is that only a few PCs activate initially which results in column formation. Thus, when columns in the cortical circuit activate, only a few PCs in each of the involved columns are activated prior to the strong inhibition that immediately follows.

Non-random features of synaptic connectivity have been reported in layer 5 PCs in the rat visual and somatosensory cortex [27,28]. Perin and colleagues speculated that elementary neuronal groups they identified in the somatosensory cortex of neonatal rats were "Lego-like" building blocks of perception [28]. Based on layer 5 pyramidal cell (PC) recordings, they identified cell assemblies in microcircuits arranged as small world networks without hubs. These kinds of networks would enable the self-organization necessary for dynamic columns. The assemblies were interlaced with other assemblies in the same space, and synaptic clusters were separated by a mean distance of 100 to 125 μm that extended beyond individual minicolumns. These clusters extended across distances equivalent to the diameter of a functional cortical column. In their view it was possible that acquired memory involved combining these elementary assemblies into unique superassemblies. They also identified three- and four-neuron motifs consistent with other findings of similar motifs in rat visual cortex [27]. In this work on rat visual cortex, strongly connected neurons were more likely to be connected reciprocally than those with weaker interconnections. These interconnected networks were found to occur more often in three-cell motifs than would be expected in a randomly connected network. Thus, these authors considered this to be a skeleton of stronger connections in a sea of weaker ones, and suggested this sparse skeleton may drive the dynamics of the neural network [27].

Despite evidence that barrel cortex neuronal spatial organization across layers is on a columnar scale [see 29 for an excellent review of barrel cortex function], there is only sparse activation of layer 2/3 PCs within barrel columns [30–35]. Lefort et al. [33] reported their network simulations indicated that synchronous action potentials in a few neurons may be sufficient to propagate neural activity. Avermann et al. [30] combined optogenetic stimulation and whole cell recordings with computational modeling tied to layer 2/3 of mouse barrel cortex. They concluded that fast spiking (FS) GABAergic neurons might contribute to driving the sparse coding in the excitatory neurons. This evidence indicates that even in regions with a clear columnar organization, there is relatively sparse activity. Therefore, similarly sparse levels of activity might be sufficient for more dynamically-organized columns to form, represent information, and propagate that information.

If this hypothesis about dynamically-organized columns is true, then the degree to which there

is a clear anatomical columnar organization in a specific cortical region in a specific species could be related to the nature of processing needed in that region on both developmental and evolutionary timescales. For example, dynamic columns that form repeatedly due to environmental pressures and that impart a survival advantage would be expected to develop clearer anatomical connections that are indicative of a stable columnar organization. Interestingly, in rat visual cortex, there does not appear to be a discernable local columnar structure as is observed in barrel cortex based on layer 2/3 neuronal responses. For example, Ohki, et al. [36] found that in rat primary visual cortex neurons had robust orientation selectivity, but neighboring neurons often responded to different orientations. This is in contrast to cat visual cortex in which functional maps were organized at a fine scale, with columnar borders one to two cells wide. They suggested that well-ordered cortical maps in the cat might have an advantage in sharpening visual responses. If that is accurate and the concept of overlapping columns is applied, then it may be that there are actually dynamic columns in the rat primary visual cortex that overlap (accounting for different orientations in neighboring neurons) because segregated columns may hold no evolutionary advantage. The evolutionary advantage of sharp responses in completely segregated barrel columns may explain why columns may overlap in one primary sensory cortical area and not in another in the rat. However, there is also some suggestion of possible overlapping columns in barrel columns because it has been shown that there is orientation specificity of only some PCs in a given barrel column [37]. In other species, such as the cat, discrete columns may exist in both visual [36] and somatosensory [38] primary receiving areas because both provide an advantage.

Another aspect contributing to apparent size differences in columns based on location maybe related to simultaneous versus sequential processing. The simultaneous nature of processing in the parietal lobe means that multiple columns in the primary somatosensory receiving area activate together. If this co-activation represents a repeated pattern there are horizontal connections among the individual columns. Those columns involving adjacent areas in the cortex then give the appearance of a larger column despite this apparent large column actually being multiple columns. The connections of these columns to the primary motor columns also means that repeated coordinated movements involves multiple motor columns that activate simultaneously. Again, despite there being individual action (i.e., primary motor) columns activated, the simultaneous activation of these columns may give an appearance of a larger column. In contrast, auditory columns are sequential in nature which means only one is activated at a time. The result is that an auditory column may appear smaller because it has no other simultaneously active horizontally connected columns in close proximity.

Up to this point in the discussion, the focus has been on evidence for overlapping dynamic columns without regard to the mechanisms that would enable such columns to form dynamically. One potential mechanism is the role of gamma oscillations related to GABAergic inhibition. Two classes of cortical inhibitory interneurons show a pattern of connectivity consistent with dynamic as opposed to static structural column formation. These are the parvalbumin-expressing (PV) and somatostatin-expressing (SOM) interneurons. Packer and Yuste [39] examined layers 2/3 and 5 mouse somatosensory and frontal neocortex. There was locally dense connectivity from PV interneurons across cortical layers onto PCs. In some cases all nearby PV interneurons contacted every local PC examined. There was no evidence of connection specificity. The authors concluded that the results support a blanket of inhibition onto local PCs as a canonical feature in neocortical microcircuits. In a similar study examining SOM interneurons, Fino and Yuste [40] found that in layer 2/3 of mouse frontal cortex most SOM interneurons are locally connected to every sampled pyramidal cell. Moreover, inhibitory connections to neighboring PCs were similar, regardless of the

connectivity amongst the PCs themselves. The authors noted that this connectivity pattern suggests that these interneurons serve to locally control PCs without any computational function. In this case, neighboring excitatory and inhibitory neurons have overlapping but not identical connectivity patterns. As in the Packer and Yuste [39] study, the effect is that the SOM and PV interneurons extend a blanket of inhibition throughout the local circuit. In this case, each neuron defines its own circuit based on its distinct efferent and afferent connections.

The purpose of this blanket inhibition in terms of dynamic columns is to initiate the synchronization of a column's pyramidal network. The most common SOM cortical interneuron, the Matinotti cell (MC), has been shown to respond to respond to simultaneous brief bursts of action potentials in as few as four PCs. The MC's response to this activity was sufficient to exert inhibition on all neighboring PCs within a column [41]. This inhibition provides a mechanism for the initiation of synchronization of the column's PC network via a mechanism such as that found in pyramidal interneuron gamma (PING) models [42,43] and described in a later section.

Insight into the purpose of this synchronization mechanism comes from studies of gamma frequency stimulation (40 Hz). Externally applied gamma frequency stimulation has been shown to activate a restricted area approximately the width of a cortical column while low frequency (10 Hz) activates a larger cortical area [41]. Additionally, Hirata and Sawaguchi [44] noted stimulation to the middle layer of macaque prefrontal cortex resulted in activity organized into columns. Importantly, different columnar activities with only slight overlaps were induced by stimulation of different sites in the same brain slice. This evidence suggests that gamma frequency oscillations are necessary for the formation of dynamic columns.

If gamma oscillations serve to dynamically organize the column, then these oscillations should also occur whenever a column is formed and strengthened. In their review of early gamma oscillation (EGO) studies, Khazipov et al. [45] suggested gamma oscillations guide barrel map formation during the critical developmental period. This suggestion was supported by Yang et al. [2] in an in vivo study using voltage-sensitive dye imaging and extracellular recordings of newborn rats. Both spontaneously occurring and stimulation-induced gamma bursts followed by longer spindle bursts were topographically organized in functional cortical columns. Simultaneous activation of the ventral posterior medial nucleus of the thalamus occurred along with activation in cortical columns. Minlebaev et al. [46] found that EGOs allowed vertical synchronization between topographically aligned thalamic and cortical neurons, and at the end of the second postnatal week adult gamma oscillations emerge to allow horizontal synchronization in the cortex. This evidence indicates that gamma oscillations serve to form and synchronize not only columns but also circuits of columns.

Furthermore, there is some evidence that the formation of columns occurs through the synchronization of only the outer cells. A modeling study of the dynamics of interacting neuronal populations provides insight into self-organized near zero-lag synchronicity. In their investigation on the influence of long conduction delays, Vicente et al. [47] employed simulations with networks of Hodgkins-Huxley neurons in integrate and fire models. In these simulations, two outer neurons (or populations) were connected to a common neuron (or population). Both with three cell circuits and three network population circuits, synchrony developed for only the outer neurons and populations, while the inner neurons were asynchronous. In relation to the studies showing three- or four-neuron motifs in which the clusters extend the diameter of a functional column [27,28], activation of the network is expected to lead to the synchronization of only the outermost clusters [41]. In other words, the outermost populations connect to the inner populations but only the outer populations synchronize. In fact, with repeated activation, the inner populations would become more asynchronous [48].

In total, the foregoing studies support the proposition that sparsely distributed small networks of pyramidal cells initiate synchronization of the outermost minicolumns in dynamically formed columns. As will be discussed in more detail, this process requires the type of inhibitory interneuron connectivity within minicolumns that is characteristic of the cortex. To summarize, local excitatory and inhibitory neuronal interactions are designed to control dynamic cortical column formation which is associated with gamma frequency synchronization. Because the column is a discrete bit, there is no information processing that occurs within the column. The activation of the column itself is the key bit of processing with more complex information processing occurring via the circuits of columns in a coding (lower-order to higher-order) and decoding (higher-order to lower-order) fashion. Thus, GABA inhibition in the cortex has local effects directed toward column formation, and columns form in order to form synchronized circuits responsible for reception, processing, and responses. The next section discussed the evidence for discrete, gamma oscillation-induced dynamic columns as the bits in cortical circuits.

Circuits of synchronized columns

As has been noted in literature reviews, there have been studies indicating that gamma-band synchronization is involved in cortical circuits [49–51]. There have been frequent discussions of local field potential (LFP) and recruitment of neuronal groups, although there is only rare mention that these signals may correspond to the column. If the column is the cortical information bit involved in multiple column circuits, then three properties should hold. First, there should be evidence of gamma-based synchrony in columns. Second, there should be evidence of discrete activation based on gamma frequency synchronization. Third, there should also be evidence for consistent activation of downstream columns based on that same frequency. In relation to this latter point, initial phase locking of distributed columns occurs at the gamma frequency, although subsequent phase locking is expected in all frequency ranges due to the strengthening synaptic interconnections.

In terms of evidence for gamma-based synchrony in columnar units, an early study that demonstrated localized gamma-band synchrony in vertical columns in the suprasylvian gyrus of cats was done by Steriade and Amzica [52]. Using brief pedunculopontine tegmental nucleus stimulation, synchronized gamma oscillations occurred in phase from the surface to the deepest layers within the columns. In relation to mouse auditory cortex, Guo et al. [10] provided evidence that in the core region there is precise tonotopic organization based on multiple unit recordings. This organization was found in the auditory cortex in all states of consciousness and based upon synchronized electrical activity observed across all cortical layers and in a columnar fashion. It was noted that in the superficial and deep layers that a substantial minority of recording sites were driven by pure tones but showed no discernible tonotopic organization which the authors suggested might be a function of cross-columnar connections outside the thalamic input layers.

There is also evidence that this column-based activity is encoding information in a discrete fashion. Similar to the current paper's proposal that the column is the bit of cortical processing, Loebel et al. [53] proposed a model in which each iso-frequency column involves a recurrent neural network. The networks are proposed to emit population spikes in which the majority of neurons synchronously fire for a brief period with subsequent short-term depression. In response to auditory stimuli, the population spikes involve lateral connections along primary auditory cortex, or core region. This involves high speed, temporally precise synchronized population spikes from the involved columns.

In a separate study of mouse auditory cortex employing two-photon calcium imaging, Bathellier et al. [54] provided evidence of discrete dynamics in auditory processing. Neurons in layer 2/3 were recorded. A characteristic finding was that a large fraction of neurons fired synchronously in short population events both spontaneously and in sound evoked response. The authors found that the auditory cortex is comprised of partially overlapping subnetworks with discrete local response patterns. Their observations were consistent with a columnar organization, noting the possibility the discrete response modes might be specific to the supragranular layers. In their discussion, the authors suggest that the discrete network dynamics may act in a binary manner of categorization such that higher-order categories are built on a hierarchy of lower-order categories. They further note the lower-order categories arise in primary sensory areas and that discrete representations (e.g., phonemes as discrete sound categories) might be essential for cognitive functions such as language processing.

Finally, there is also evidence that the synchronized activity enables the formation of multiple column circuits. In a recent study of gamma oscillatory activity between V1 and V2 in the macaque, there is support for feed-forward and layer-specific connectivity [55]. In response to gratings of varying contrasts, gamma frequency increased with stimulus contrast with coherence maintained between the neural populations in these regions. Thus, it was shown that gamma coherence can occur across regions despite large stimulus-induced and time-dependent changes in gamma frequency.

In another study, Ince et al. [56] evaluated neural responses to natural sounds in the Macaque. Their results supported the view that a small population of neurons communicates considerable information and that high temporal precision within circuits of such populations is important. In a study analyzing zero lag gamma events in freely moving rats, the events were associated with local modules (based on spacing of 1.5 mm separation of microelectrodes) [57]. They found that gamma events recorded in different brain regions occurred with zero-time lag, as well as within an event time window during the resting state. This finding was considered to indicate coherence-based connectivity. These are just a sample of studies showing temporally precise communication among small groups of neurons consistent with gamma-based synchronization of circuits of columns.

Based on the weak PING model only a few excitatory neurons can initiate gamma synchronization [42,43]. Thus, the overlapping subnetworks involved in discrete local response patterns [54], the three- and four-neuron motifs [27,28] in layer 2/3, and the dense interneuron to pyramidal cell connections [39,40] provide a picture of how overlapping columns can operate. The discussion now turns to the details of how gamma synchronization occurs within columns in order to enable the formation of dynamic circuits of columns.

Receptors, neurons, and gamma-band synchronization

There have been recent detailed reviews on the biological processes involved in gamma oscillations in the cerebral cortex [58,59]. As noted in these papers, there are competing models and a number of questions remain. For the purposes of the current paper, general information will be presented with the goal of explaining how the column model fits with a weak PING model in which gamma oscillations are based on PC driven activation of interneurons that then inhibit the PC population [42,43]. PING models differ from models that rely on interneurons alone such as the interneuron gamma (ING) model.

Table 2. Neuron/Receptor Function in Dynamic Cortical Column Formation

Cell/Receptor Type	Function in Column Formation and Strengthening
	Column and Columnar Circuit Formation
AMPARs	AMPARs of the PCs are associated with initial propagation of activation to downstream columns providing the activation of PCs that drives the inhibitory interneurons that lead to gamma oscillations via a PING model.
PV	PV interneurons are involved in the synchronization of the column "signal" by promoting gamma oscillations via inhibitory connections with PCs (as in PING models).
SOM	SOM interneurons influence the horizontal spread of inhibition to surrounding columns. Inhibition around a newly formed column enhances strengthening of the memory. The columnar coherence (the "signal") would be enhanced through the inhibition of overlapping and adjacent columns ("noise").
SBCs	SBC interneurons establish the column boundary via disinhibitory control of layer 5 PCs via inhibitory connections to layers 2/3 interneurons would otherwise inhibit layer 5 PCs. Leads to activation of NMDARs and strengthening of columns as detailed below.
	Column Strengthening/Consolidation
NMDARs	NMDARs of the PCs are involved in the synaptic strengthening, or memory consolidation processes. NMDAR calcium permeability means that the NMDAR-mediated currents provide longer excitability durations necessary for synaptic strengthening.
VIP	VIP interneurons control both SOM and PV cells by inhibition of other inhibitory interneurons (i.e., disinhibitory control). VIP interneurons inhibit some of the PV interneurons for a short duration and a larger percentage of the SOM interneurons for a slightly longer duration, allowing disinhibition of the longer duration NMDARs to serve as the strengthening connections of the proposed peripheral minicolumn PCs to their targets.
NGC	Elongated neurogliaform cells provide complete inhibition of all neuronal activity in the projection area of their axonal field. Via inhibition of all other interior minicolumns and minicolumns from overlapping columns, they increase the signal-to-noise ratio allowing newly formed columns to strengthen.

There are several aspects involved in the posited column circuitry. Pyramidal neurons in layer

2/3 provide intra-areal horizontal activation, while layer 5 pyramidal neurons provide long range connections and can enhance layer 2/3 activity [60]. The three main classes of inhibitory cortical neurons are PV-expressing, SOM-expressing, and vasoactive intestinal polypeptide (VIP)-expressing interneurons. The two glutamate receptors are the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) type and the N-methyl-D-aspartate receptor (NMDAR).

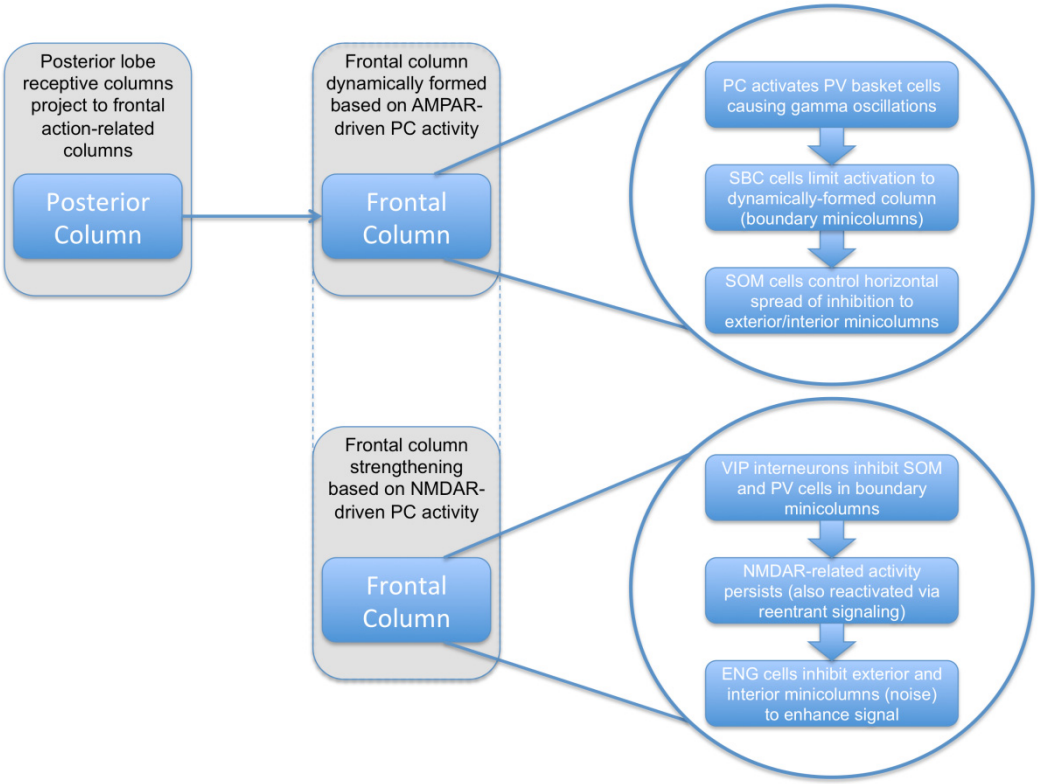

Figure 1. Diagram showing dynamic formation of frontal column in DSM model along with role of different neuron types in the process of dynamic column formation from minicolumns and column strengthening.

Moss [14] discussed a general columnar design based on the six cortical layers for heuristic purposes. It was acknowledged that there were no definitive works of the afferent and efferent connections of the cellular structure of the cortical layers. However, the design was such that the discrete column was activated and then inhibited once its afferent information was sent to downstream columns. In relation to the model, there are two important aspects. First, a column sends the primary signal to activate downstream columns. The proposed idea described in this section is that AMPARs are associated with this initial propagation to downstream columns. Second, there are continued processes to allow for strengthening (i.e., memory consolidation) of synaptic connections among the newly created column circuit. Thus, there should be evidence of immediate column activation allowing immediate information transfer, followed by inhibition to prevent further transmission, but local signs in the column of continued activation involved with the consolidation process. The second part of the proposed idea described here is that NMDARs are more involved in the synaptic strengthening, or memory, process. Figure 1 provides an overview of the cells and

processes involved in the formation and strengthening of columns, and Table 2 provides a more detailed summary of the function of each cell type in this process.

Signal propagation enabled by AMPARs

There appears to be consensus on several points in models of gamma oscillations. First is that gamma-aminobutyric acid (GABA) receptor-mediated inhibition is necessary for gamma oscillations [58]. The hypothesis that fast spiking (FS), PV basket cells promote gamma oscillations has substantial support. ING models have shown that only mutually connected inhibitory interneurons are required for the emergence of gamma oscillations, provided there is sufficient drive to induce spiking in the interneurons and a time constant provided by GABA [61]. PING models are based on the reciprocal connections between groups of regular spiking (RS) pyramidal excitatory neurons and inhibitory neurons. In PING models, the fast excitation alternates with the delayed feedback inhibition. Whereas strong PING models involve a large population of excitatory neurons, the weak PING model is based on sparse activation of pyramidal cells [42,43].

A recent study [62] has shown that interactions between supragranular and infragranular layers are required for activity propagation in the cortex. It was found that thalamic sensory input leads to a sequence of activation of layer 4 to layer 2/3 to layer 5 followed by horizontal propagation. Layer 2/3 had an upstate in 20 to 30 ms, with layer 5 activating 10 ms later. This *in vitro* study found activation of an adjacent column in 75 ms, indicating a propagation velocity of 20 mm/s. They noted much faster speeds (100 mm/s) have been reported *in vivo* [63].

This transmission model provides an indication that the initial discrete “bit” is formed in less than 50 ms with it conveying its information immediately. This time frame is consistent with one model of synchronization speed based on 20 to 50 ms for typical membrane constants [64]. Thus, a logical conclusion is that continued activity in newly formed columns beyond the primary signal conductance is directed toward consolidation of the new column, in conjunction with its cortical and subcortical connections. If accurate, this can provide insight into the various roles of receptor and cell types within the column, as well as in the spontaneous neocortical activity patterns.

This proposal is consistent with the duration of currents in AMPARs. As noted by Gonzalez-Burgos and Lewis [65], AMPARs appear to provide the necessary phasic excitation that drives the PV neurons. This conclusion is based on the fact that NMDARs have voltage-dependent magnesium blocks that make them unlikely to initiate the required neuronal excitation. Moreover, there are two other important characteristic differences between NMDARs and AMPARs. NMDARs generate significantly longer duration currents (100–400 ms) than AMPARs (2–10 ms). This difference in duration suggests the AMPARs are likely responsible for the initial conductance of the information bit signal due to fast but brief activation. A second point is that in contrast to most AMPAR channel subtypes, NMDAR channels are highly permeable to calcium. This permeability is important in the NMDAR-dependent changes in synaptic strength because the high calcium influx activates calcium-calmodulin kinase II-alpha (CaMKII). Overall, this calcium permeability means that the NMDAR-mediated currents provide longer excitability durations necessary for synaptic strengthening. In terms of the DSM, NMDARs therefore allow for the posited consolidation process to strengthen column boundaries and associated connections.

Column consolidation enabled by NMDARs

There is some support in the literature for this consolidation-enabling role of NMDARs. Wang

et al. [66] discussed the research supporting the requirements of post-learning NMDARs and CaMKII reactivations in systems-level memories. They felt that this reactivation may lead to synaptic reentry reinforcement (SRR) in which multiple rounds of NMDAR-mediated synaptic modifications occur [67]. The SRR hypothesis indicated the hippocampus goes through reactivation during consolidation and can act as a coincidence regenerator. This leads to the simultaneous reactivation and strengthening of connections of cortical neurons in the different sensory modules involved in the original cortical processing.

The DSM view of consolidation deviates from that hypothesis in a couple of important ways. First, it clarifies that the hippocampus is not the source of new memories later transferred to the cortex. The same columns involved in the original cortical processing are both the short-term and long-term memory with the hippocampus merely providing the cyclic activity to the various columns comprising the memory. In the case of information streams in different cortical areas leading to the single highest-order column in each of those streams, then those highest-order columns project to and form the new temporal lobe cortical column that associates those different information streams. The hippocampus, via its involvement of only a few cells capable of long term potentiation and depression, is best capable of supplying the thalamic and cortical circuit reactivation which in turn leads to the synaptic strengthening at the cortical level. Notably, because the single hippocampus neurons are in the circuit line, they activate any time the cortical columns tied to a given memory activate. This gives the appearance via stimulus-induced activation that single hippocampal neurons have encoded the memory (e.g., a Jennifer Anniston cell, place cells) even though the memory has always been stored in the cortical circuit.

Therefore the NMDARs are critical to the strengthening of the circuits of cortical columns that are the key feature of neural information processing in the DSM. There is also research that links NMDARs to strengthening of circuits. Luczak and MacLean [68] provided a review of studies on the similar sequential order of neuronal activation in the neocortex spontaneously and in response to stimulus input. They suggested that the similarity of evoked and spontaneous activity results from both evoked and spontaneous activity playing out on the same cortical architecture. Similarly, Bermudez Contreras and colleagues [69] found that repeated tactile and auditory stimulation evoked unique sequential neural firing patterns in the somatosensory and auditory cortices in urethane-anesthetized rats. The same pattern recurred during subsequent spontaneous activity. Notably, an NMDAR antagonist blocked the patterns suggesting the role of synaptic plasticity and again demonstrating the importance of NMDARs in memory consolidation. Fukushima et al. [70] found that spontaneous activity closely follows functional organization in Macaque auditory cortex. Moreover, *in vivo* two-photon imaging of mouse auditory cortex demonstrated that NMDAR-dependent spine calcium signals occurring in spontaneous up states are the same as those associated with sensory stimulation [71]. Chen et al. [71] suggest that such “patterned” calcium activity may control consolidation following the stimulation.

Based on the foregoing reviews and research studies, there is an association between NMDARs and memory consolidation. If the column is the discrete bit involved in cortical processing, then there would necessarily be a mechanism for feed-forward output to other columns and subcortical targets, followed by a separate consolidation mechanism. Based on the assumption that the outermost minicolumns are those that are the dynamic column, these are the ones that first convey the critical AMPA-regulated efferent activity and this conveyance is then followed by gamma oscillatory activity. Because it is the intersection of multiple lower-order columns’ activity that leads to the formation of a new column, then where this efferent stream of all the minicolumns of one column coincides with that of another column’s outer minicolumns, there will be the activation of the outer minicolumns of

the newly formed higher-order column. This new column's outer minicolumns immediately convey their efferent signal followed by gamma-band synchrony to stabilize the newly formed dynamic column. The stabilization process includes the rapid spread of the gamma oscillations to surrounding tissue, including the internal minicolumns of each column. To allow only the consolidation of connections of outer minicolumns to other targets, there must be mechanisms to control the horizontal spread of initial AMPAR-based activity. This mechanism is consistent with the quick PC-PV neuron gamma-based feed-forward inhibition found in PING models. In addition, there must be subsequent reactivation of the outer minicolumns with inhibition of all other neurons located both internally and externally to allow synaptic strengthening to occur only in the outer minicolumns. The evidence for these two mechanisms (PC-PV inhibition and outer minicolumns strengthening) is now presented.

SOM interneurons appear to largely influence the horizontal spread of inhibition [72]. This group of interneurons may serve to determine the spread of inhibition to surrounding columns. Interestingly, in human intracranial recordings the inhibitory network activity was been shown to occur over distances beyond a column (>4 mm) in comparison to local excitatory interactions (around 1 mm) [73]. Moss [14] suggested that inhibition around a newly formed column enhances strengthening of the memory. In this case, the columnar coherence (the "signal") would be enhanced through the inhibition of overlapping and adjacent columns ("noise").

While the SOMs are providing this signal enhancement, the PV interneurons are involved in the synchronization of the column "signal" and the VIP interneurons control both sets. Recently, it has been shown that VIP interneurons specialize in the inhibition of other inhibitory interneurons (i.e., disinhibitory control). Pi et al. [74] found in mouse auditory cortex and medial prefrontal cortex that brief light stimulation of VIP interneurons had broad effects in firing rate changes of two other neuron groups. In the first group many, but not all, of the inhibited neurons were consistent with PV interneuron activity patterns. There was also a subgroup of these neurons that were initially suppressed and later activated by the VIP stimulation. Many cells in the latter group had patterns consistent with pyramidal neurons. This demonstrated an excitation-inhibition-excitation sequence in the two functionally distinct cortical regions *in vivo*. In a second condition, in vitro slice analysis provided information on SOM versus PV interneurons targeted by the VIP interneurons. Inhibitory postsynaptic currents (IPSCs) occurred in a large fraction of SOM interneurons at 40Hz (gamma frequency) with short-term synaptic depression. VIP activation resulted in IPSCs in a smaller fraction of PV interneurons and these decayed faster with stronger short-term synaptic depression than those in the SOM interneurons. These results show that the control signal from VIP interneurons lead to distinct effects on SOM and PV interneurons, supporting a distinction in function for PV and SOM interneurons. Notably, only a small fraction of pyramidal neurons responded to VIP activation, and this pattern is consistent with the sparse pyramidal neuron small networks being involved in the dynamic column being formed (the bit). Other analyses revealed that the delayed activated population consists mainly of pyramidal neurons. Although not evaluated, the longer duration of NMDAR excitation would make these the most likely candidate receptors to be involved with delayed activation.

In the absence of definitive information on all connections among all the types of cells, it is not possible to provide conclusive information on exactly how columns are formed and consolidated. However, based on the foregoing information, a possible manner of dynamic column formation will be proposed. It appears that stimulus input to layer 4 in a column leads to the targeted activation of the strongly connected motifs of a few pyramidal neurons in layers 5 and 2/3. The pyramidal neurons' axonal firing provides feed-forward extracolumnar target stimulation and activates AMPA receptors

of the PV interneurons resulting in gamma oscillations associated with further feed-forward inhibition. The RS SOM interneurons establish the horizontal limits of the gamma oscillations around a column while layer 1 single-bouquet cells (SBCs) provide the column boundary. Moss [14] proposed that layer 1 cells determine the boundary of a given column, and in the description of two novel cortical interneuron circuits, Jiang et al. [75] found that layer 1 SBC provide unidirectional inhibitory connections to layer 2/3 interneurons which affect layer 5 PCs. Notably, the only layer 5 PCs inhibited were within its own column and did not influence those in any neighboring columns. NMDARs are activated during this process. VIP interneurons inhibit some of the PV interneurons for a short duration and a larger percentage of the SOM interneurons for a slightly longer duration, allowing disinhibition of the longer duration NMDARs to serve as the primary ones involved with strengthening connections of the proposed peripheral minicolumn PCs to their targets. The latter aspect is based on the expectation that only the outermost neurons are the ones that maintain zero-lag synchronization [47].

The continued strengthening of the column would also require a longer duration inhibition mechanism. A possible candidate for longer duration inhibition in and around the column is the neurogliaform cell (NGC). These provide complete inhibition of all neuronal activity in the projection area of their axonal field, being < 200 μm [76]. This spread activated from the location of peripheral minicolumns would affect all the neurons within the column and the majority of any overlapping column's neurons. Additionally, there would be inhibition of about half the neurons in any adjacent column's neurons. Consistent with this NGC inhibitory mechanism, Jiang et al. [75] described a layer 1 circuit from the elongated NGCs that formed mutual electric and inhibitory connections with layer 2/3, and these interneuorns provided inhibition to a majority of layer 5 PCs. As opposed to the SBC intracolumnar connections, the elongated NGCs provided inhibition across multiple columns. They concluded that the suppression of the dendritic complex could effectively increase the signal-to-noise ratio by sharpening the receptive field via suppression of surrounding activity. This increased signal-to-noise ratio is exactly what is required to continue to strengthen newly formed columns.

A final note is that the PC-PV interneuron connections role appear to be a constant in quick gamma-band oscillatory activity and are unlikely to show any plasticity, being ubiquitous across the neocortex. This appears to be important because the quick feed-forward inhibition provided by this circuit is necessary for each of the overlapping columns, as would the longer duration inhibition from NGCs. In contrast, the PC-MC and PC-PC are the ones involved with synaptic plasticity of newly formed columns and responsible for the memory consolidation NMDAR-related process in conjunction with the SBCs and VIP interneurons. Support for this plasticity distinction is provided by a study [77] showing presynaptic NMDARs in neocortical microcircuits. Whereas PC-MC and PC-PC connections possess presynaptic NMDARs, these were absent in PC connections with the PV basket cells.

This section has focused on the potential role of NMDARs and AMPARs along with different interneuron types in producing the kind of dynamic column formation and strengthening proposed in the Dimensional Systems Model. There has been a detailed discussion of how this column-based model relates to the development of psychological problems, such as depression and anxiety disorders [16,25,78]. However, this kind of discussion has not been done in relation to the more serious and disabling neuropsychiatric disorders of schizophrenia and autistic spectrum disorders. Additionally, there has not been significant discussion of Alzheimer's disease. This newly developed understanding of the role of NMDARs and minicolumns in the model provides the basis for a discussion of how these serious disorders are related to disrupted column formation.

Disorders of disrupted cortical column formation

Briefly summarizing a few points will assist in understanding the implications of the current theory for schizophrenia, autism, and Alzheimer's disease. The consolidation of new cortical memories requires both formation of new columns and their interconnections. A possible manner for these dynamics was discussed, emphasizing the coordination of PCs and inhibitory interneurons. Based on the need for each component to occur for both new learning and forming memories, it is possible to see why there is evidence for the influence of each factor. In other words, it is possible that the disruption of any one of these components may lead to dysfunction. Additionally, connections to and from the hippocampus and thalamus are necessary for the system circuitry that allows the strengthening of individual dynamic columns and their connections.

Neural synchronicity abnormalities, NMDARs, and amyloid-β's effect on synaptic plasticity/loss, have been implicated as playing a role in Alzheimer's disease [51,79–81]. In relation to autism, neural oscillatory patterns [82] and NMDARs [83] have received attention. Schizophrenia research has noted involvement of NMDARs, PV interneurons, and gamma oscillations [65]. In addition to each of these, it seems likely that the other factors influencing posited dynamic column formation may play a role in one or more of these disorders.

The current theory suggests outer minicolumns are critical for column integrity. However, there has been no discussion as to how size and spacing of minicolumns may interact with dynamic column formation. To the knowledge of the current authors, there are no data available due to the novelty of the concept. However, altered or abnormal spacing of minicolumns have been mentioned in relation to schizophrenia [84,85], autism [86,87], and Alzheimer's disease [88,89]. In addition to possible dynamic column formation problems, size and spacing of minicolumns may also have an effect on the ability to form long range inter-column connections. For example, there may not be the needed volume or size matching in more distal projection targets to allow a new column to form or be consolidated (e.g., reentrant processes). Thus, minicolumns spacing difference could explain the impaired connectivity between frontal and posterior cortical regions in autism [90], as well as the frontal lobe-related cognitive problems in schizophrenia [91]. In the case of Alzheimer's disease, the thinning of minicolumns [89] may contribute to early loss of new column formation and the late loss of the integrity of dynamic columns that have existed for years. Briefly summarizing a few points will assist in understanding the implications of the current theory for schizophrenia, autism, and Alzheimer's disease. The consolidation of new cortical memories requires both formation of new columns and their interconnections. A possible manner for these dynamics was discussed, emphasizing the coordination of PCs and inhibitory interneurons. Based on the need for each component to occur for both new learning and forming memories, it is possible to see why there is evidence for the influence of each factor. In other words, it is possible that the disruption of any one of these components may lead to dysfunction. Additionally, connections to and from the hippocampus and thalamus are necessary for the system circuitry that allows the strengthening of individual dynamic columns and their connections.

2. Conclusions

The current paper has provided a description of the microcircuitry processes that support the overlapping column aspects of the Dimensional Systems Model and the applied Clinical Biopsychology Model [14–16]. There are obviously a number of areas in which further clarifications

are needed and confirmatory evidence is required. It is believed that at the macro and micro levels the models have now been described, *a priori* research hypotheses and associated studies can be designed at all levels. As when any grand theory is proposed in the presence of so much that is unknown, it is impossible to know how much will survive once it has been subjected to the test by fire involving the scrutiny of researchers with access to all the current and developing technologies. However, it appears the field of neuroscience is ripe for a different way of organizing the data in anticipation of the day that the human brain will finally understand the human brain.

Conflict of interest

No conflicts exist.

References

1. Gray CM, Singer W. (1989) Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proc Natl Acad Sci* 86: 1698–1702.
2. Yang J-W, An S, Sun J-J, Reyes-Puerta V, Kindler J, Berger T, Kilb W, Luhmann HJ. (2013) Thalamic Network Oscillations Synchronize Ontogenetic Columns in the Newborn Rat Barrel Cortex. *Cereb Cortex* 23: 1299–1316.
3. Steriade M, Amzica F. (1996) Intracortical and corticothalamic coherency of fast spontaneous oscillations. *Proc Natl Acad Sci* 93: 2533–2538.
4. Singer W. (1999) Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 24: 49–65.
5. Fries P. (2009) Neuronal Gamma-Band Synchronization as a Fundamental Process in Cortical Computation. *Annu Rev Neurosci* 32: 209–224.
6. Ray S, Maunsell, JHR. (2010) Differences in Gamma Frequencies across Visual Cortex Restrict Their Possible Use in Computation. *Neuron* 67: 885–896.
7. Jia X, Xing D Kohn A. (2013) No Consistent Relationship between Gamma Power and Peak Frequency in Macaque Primary Visual Cortex. *J Neurosci* 33: 17–25.
8. Burns SP, Xing D, Shapley RM. (2011) Is Gamma-Band Activity in the Local Field Potential of V1 Cortex a "Clock" or Filtered Noise? *J Neurosci* 31: 9658–9664.
9. Merker B. (2013) Cortical gamma oscillations: the functional key is activation, not cognition. *Neurosci Biobehav Rev* 37: 401–417.
10. Guo W, Chambers AR, Darrow KN, et al. (2012) Robustness of Cortical Topography across Fields, Laminae, Anesthetic States, and Neurophysiological Signal Types. *J Neurosci* 32: 9159–9172.
11. Mountcastle VB. (1957) Modality and topographic properties of single neurons of cat's somatic sensory cortex. *J Neurophysiol* 20: 408–434.
12. Mountcastle VB. (1997) The columnar organization of the neocortex. *Brain* 120: 701–722.
13. Horton JC Adams DL. (2005) The cortical column: a structure without a function. *Philos Trans R Soc B Biol Sci* 360: 837–862.
14. Moss RA. (2006) Of bits and logic: Cortical columns in learning and memory. *J Mind Behav* 27: 215–246.
15. Moss RA, Hunter BP, Shah D Havens TL. (2012) A Theory of Hemispheric Specialization Based on Cortical Columns. *J Mind Behav* 33: 141–172.
16. Moss RA. (2013) Psychotherapy and the Brain: The Dimensional Systems Model and Clinical

Biopsychology. *J Mind Behav* 34: 63–89.
17. Moss RA. (2013) Gamma-band Synchronization & Cortical Columns. *Neuropsychotherapist* 3: 126–127.
18. Luria AR. (1966) Higher cortical functions in man. New York: Basic Books.
19. Lezak MD, Howieson DB, Loring DW and Hannay HJ. (2004) *Neuropsychological Assessment* 4 Eds., Oxford: Oxford University Press.
20. Calvin W. (1995) Cortical columns, modules, and Hebbian cell assemblies. In *Handbook of brain theory and neural networks*, Arbib MA. Author. Cambridge, MA: MIT Press. 269–275.
21. Tulving E, Thomson DM. (1973) Encoding specificity and retrieval processes in episodic memory. *Psychol Rev* 80: 352–373.
22. Rissman J Wagner AD. (2012) Distributed representations in memory: Insights from functional brain imaging. *Annu Rev Psychol* 63: 101–128.
23. Polyn SM, Natu VS, Cohe JD and Norman KA. (2005) Category-specific cortical activity precedes retrieval during memory search. *Science* 310: 1963–1966.
24. Gazzaniga MS. (2002) Consciousness. In *Encyclopedia of the human brain,* Ramachandran VS, Eds. New York: Academic Press, 31–35.
25. Moss RA. (2007) Negative emotional memories in clinical treatment: Theoretical considerations. *J Psychother Integr* 17: 209–224.
26. Olshausen BA Field DJ. (2004) Sparse coding of sensory inputs. *Curr Opin Neurobiol* 14: 481–487.
27. Song S, Sjöström PJ, Reigl M, Nelson S Chklovskii DB. (2005) Highly Nonrandom Features of Synaptic Connectivity in Local Cortical Circuits. *PLoS Biol* 3: e68.
28. Perin R, Berger TK Markram H. (2011) A synaptic organizing principle for cortical neuronal groups. *Proc Natl Acad Sci* 108: 5419–5424.
29. Feldmeyer D, Brecht M, Helmchen F, Petersen CCH, Poulet JFA, Staiger JF, Luhmann HJ Schwarz C. (2013) Barrel cortex function. *Prog Neurobiol* 103: 3–27.
30. Avermann M, Tomm, C, Mateo C, Gerstner W Petersen CCH. (2012) Microcircuits of excitatory and inhibitory neurons in layer 2/3 of mouse barrel cortex. *J Neurophysiol* 107: 3116–3134.
31. Crochet S, Poulet JF, Kremer Y, Petersen CC. (2011) Synaptic Mechanisms Underlying Sparse Coding of Active Touch. *Neuron* 69: 1160–1175.
32. Kerr JN, de Kock CP, Greenberg DS, Bruno RM, Sakmann B, Helmchen F. (2007) Spatial Organization of Neuronal Population Responses in Layer 2/3 of Rat Barrel Cortex. *J Neurosci* 27: 13316–13328.
33. Lefort S, Tomm C, Floyd Sarria JC, Petersen CC. (2009) The Excitatory Neuronal Network of the C2 Barrel Column in Mouse Primary Somatosensory Cortex. *Neuron* 61: 301–316.
34. O'Connor DH, Peron SP, Huber D, Svoboda K. (2010) Neural Activity in Barrel Cortex Underlying Vibrissa-Based Object Localization in Mice. *Neuron* 67: 1048–1061.
35. Yassin L, Benedetti BL, Jouhanneau JS, Wen JA, Poulet JF, Barth AL. (2010) An Embedded Subnetwork of Highly Active Neurons in the Neocortex. *Neuron* 68: 1043–1050.
36. Ohki K, Chung S, Ch'ng YH, Kara P, Reid RC. (2005) Functional imaging with cellular resolution reveals precise micro-architecture in visual cortex. *Nature* 433: 597–603.
37. Bruno RM, Khatri V, Land PW, Simons DJ. (2003) Thalamocortical angular tuning domains within individual barrels of rat somatosensory cortex. *J Neurosci* 23: 9565–9574.
38. Favorov OV, Diamond ME, Whitsel BL. (1987) Evidence for a mosaic representation of the body surface in area 3b of the somatic cortex of cat. *Proc Natl Acad Sci* 84: 6606–6610.
39. Packer AM, Yuste R. (2011) Dense, Unspecific Connectivity of Neocortical

Parvalbumin-Positive Interneurons: A Canonical Microcircuit for Inhibition? *J Neurosci* 31: 13260–13271.
40. Fino E, Packer AM, Yuste R. (2013) The logic of inhibitory connectivity in the neocortex. *The Neuroscientist* 19: 228–237.
41. Berger TK, Silberberg G, Perin R, Markram H. (2010) Brief Bursts Self-Inhibit and Correlate the Pyramidal Network. *PLoS Biol* 8: e1000473.
42. Börgers C, Talei Franzesi G, LeBeau FEN, Boyden ES, Kopell NJ. (2012) Minimal Size of Cell Assemblies Coordinated by Gamma Oscillations. *PLoS Comput Biol* 8: e1002362.
43. Börgers C, Epstein S, Kopell NJ. (2005) Background gamma rhythmicity and attention in cortical local circuits: A computational study. *Proc Natl Acad Sci USA* 102: 7002–7007.
44. Hirata Y, and Sawaguchi T. (2008) Functional columns in the primate prefrontal cortex revealed by optical imaging in vitro. *Neurosci Res* 61: 1–10.
45. Khazipov R, Minlebaev M Valeeva G. (2013) Early gamma oscillations. *Neuroscience* 250: 240–252.
46. Minlebaev M, Colonnese M, Tsintsadze T, Sirota A, Khazipov R. (2011) Early Gamma Oscillations Synchronize Developing Thalamus and Cortex. *Science* 334: 226–229.
47. Vicente R, Gollo LL, Mirasso CR, Fischer I Pipa G. (2008) Dynamical relaying can yield zero time lag neuronal synchrony despite long conduction delays. *Proc Natl Acad Sci* 105: 17157–17162.
48. Gruber T Müller MM. (2002) Effects of picture repetition on induced gamma band responses, evoked potentials, and phase synchrony in the human EEG. *Cogn Brain Res* 13: 377–392.
49. Ahmed OJ Cash SS. (2013) Finding synchrony in the desynchronized EEG: the history and interpretation of gamma rhythms. *Front Integr Neurosci* 7: 58.
50. Isaacson JS, Scanziani M. (2011) How Inhibition Shapes Cortical Activity. *Neuron* 72: 231–243.
51. Uhlhaas P, Pipa G, Lima B, Melloni L, Neuenschwander S, Nikolić D, Singer W, Uhlhaas PJ, Pipa G, Lima B, et al. (2009) Neural synchrony in cortical networks: history, concept and current status. *Front Integr Neurosci* 3: 17.
52. Amzica F Steriade M. (1996) Progressive cortical synchronization of ponto-geniculo-occipital potentials during rapid eye movement sleep. *Neuroscience* 72: 309–314.
53. Loebel A, Nelken I Tsodyks M. (2007) Processing of sounds by population spikes in a model of primary auditory cortex. *Front Neurosci* 1: 1.
54. Bathellier B, Ushakova L Rumpel S. (2012) Discrete Neocortical Dynamics Predict Behavioral Categorization of Sounds. *Neuron* 76: 435–449.
55. Roberts MJ, Lowet E, Brunet NM, Ter Wal M, Tiesinga P, Fries P De Weerd P. (2013) Robust Gamma Coherence between Macaque V1 and V2 by Dynamic Frequency Matching. *Neuron* 78: 523–536.
56. Ince RAA, Panzeri S Kayser C. (2013) Neural Codes Formed by Small and Temporally Precise Populations in Auditory Cortex. *J Neurosci* 33: 18277–18287.
57. Bragin A, Almajano J, Kheiri F, Engel JJ. (2014) Functional Connectivity in the Brain Estimated by Analysis of Gamma Events. *PLoS ONE* 9: e85900.
58. Buzsáki G, Wang XJ. (2012) Mechanisms of Gamma Oscillations. *Annu Rev Neurosci* 35: 203–225.
59. Wang L, Liu X, Guise KG, Knight RT, Ghajar J Fan J. (2010) Effective Connectivity of the Fronto-parietal Network during Attentional Control. *J Cogn Neurosci* 22: 543–553.
60. Douglas RJ Martin KAC. (2004) Neuronal Circuits of the Neocortex. *Annu Rev Neurosci* 27: 419–451.

61. Tiesinga P Sejnowski TJ. (2009) Cortical Enlightenment: Are Attentional Gamma Oscillations Driven by ING or PING? *Neuron* 63: 727–732.
62. Wester JC Contreras D. (2012) Columnar Interactions Determine Horizontal Propagation of Recurrent Network Activity in Neocortex. *J Neurosci* 32: 5454–5471.
63. Amzica F Steriade M. (1995) Short- and long-range neuronal synchronization of the slow. (< 1 Hz) cortical oscillation. *J Neurophysiol* 73: 20–38.
64. Rutishauser U, Slotine JJ Douglas RJ. (2012) Competition Through Selective Inhibitory Synchrony. *Neural Comput* 24: 2033–2052.
65. Gonzalez-Burgos G Lewis DA. (2012) NMDA Receptor Hypofunction, Parvalbumin-Positive Neurons, and Cortical Gamma Oscillations in Schizophrenia. *Schizophr Bull* 38: 950–957.
66. Wang H, Hu Y Tsien JZ. (2006) Molecular and systems mechanisms of memory consolidation and storage. *Prog Neurobiol* 79: 123–135.
67. Shimizu E, Tang YP, Rampon C Tsien J Z. (2000) NMDA Receptor-Dependent Synaptic Reinforcement as a Crucial Process for Memory Consolidation. *Science* 290: 1170–1174.
68. Luczak A and MacLean JN. (2012) Default activity patterns at the neocortical microcircuit level. *Front Integr Neurosci* 6: 30.
69. Bermudez Contreras EJ, Schjetnan AGP, Muhammad A, Bartho P, McNaughton BL, Kolb B, Gruber AJ Luczak A. (2013) Formation and Reverberation of Sequential Neural Activity Patterns Evoked by Sensory Stimulation Are Enhanced during Cortical Desynchronization. *Neuron* 79: 555–566.
70. Fukushima M, Saunders RC, Leopold DA, Mishkin M Averbeck BB. (2012) Spontaneous High-Gamma Band Activity Reflects Functional Organization of Auditory Cortex in the Awake Macaque. *Neuron* 74: 899–910.
71. Chen X, Rochefort NL, Sakmann B Konnerth A. (2013) Reactivation of the Same Synapses during Spontaneous Up States and Sensory Stimuli. *Cell Rep* 4: 31–39.
72. Shlosberg D, Buskila Y, Abu-Ghanem Y Amitai Y. (2012) Spatiotemporal alterations of cortical network activity by selective loss of NOS-expressing interneurons. *Front Neural Circuits* 6: 3.
73. Peyrache A, Dehghani N, Eskandar EN, Madsen JR, Anderson WS, Donoghue JA, Hochberg LR, Halgren E, Cash SS Destexhe A. (2012) Spatiotemporal dynamics of neocortical excitation and inhibition during human sleep. *Proc Natl Acad Sci* 109: 1731–1736.
74. Pi HJ, Hangya B, Kvitsiani D, Sanders, JI, Huang ZJ Kepecs A. (2013) Cortical interneurons that specialize in disinhibitory control. *Nature* 503: 521–524.
75. Jiang X, Wang G, Lee AJ, Stornetta RL Zhu JJ. (2013) The organization of two new cortical interneuronal circuits. *Nat Neurosci* 16: 210–218.
76. Lee CK Huguenard JR. (2011) Martinotti Cells: Community Organizers. *Neuron* 69: 1042–1045.
77. Buchanan KA, Blackman AV, Moreau AW, Elgar D, Costa RP, Lalanne T, Tudor JAA, Oyrer J and Sjöström PJ. (2012) Target-Specific Expression of Presynaptic NMDA Receptors in Neocortical Microcircuits. *Neuron* 75: 451–466.
78. Moss, R A. (2013) A Clinical Biopsychological Theory of Loss-Related Depression. *J Neuropsychother* 1: 56–65.
79. Huang, Y-J, Lin, C-H, Lane, H-Y, Tsai, G E. (2012) NMDA Neurotransmission Dysfunction in Behavioral and Psychological Symptoms of Alzheimer's Disease. *Curr Neuropharmacol* 10: 272–285.
80. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso,PJ, Gouras GK, et al. (2005) Regulation of NMDA receptor trafficking by amyloid-β. *Nat Neurosci* 8: 1051–1058.

81. Stam CJ, van Walsum, A M van C, Pijnenburg YA, Berendse HW, de Munck JC, Scheltens P, van Dijk BW. (2002) Generalized synchronization of MEG recordings in Alzheimer's disease: evidence for involvement of the gamma band. *J Clin Neurophysiol* 19: 562–574.
82. Gandal MJ, Edgar JC, Ehrlichman RS, Mehta M, Roberts TPL, Siegel SJ. (2010) Validating γ Oscillations and Delayed Auditory Responses as Translational Biomarkers of Autism. *Biol Psychiatry* 68: 1100–1106.
83. Tarabeux J, Kebir O, Gauthier J, Hamdan FF, Xiong L, Piton A, Spiegelman D, Henrion É Millet, B Fathalli, F et al. (2011) Rare mutations in N-methyl-D-aspartate glutamate receptors in autism spectrum disorders and schizophrenia. *Transl Psychiatry* 1: e55.
84. Chance SA, Casanova MF, Switala AE, Crow TJ. (2008) Auditory cortex asymmetry, altered minicolumn spacing and absence of ageing effects in schizophrenia. *Brain* 131: 3178–3192.
85. Di Rosa E, Crow TJ, Walker MA, Black G, Chance SA. (2009) Reduced neuron density, enlarged minicolumn spacing and altered ageing effects in fusiform cortex in schizophrenia. *Psychiatry Res* 166: 102–115.
86. Casanova MF, Kooten IAJ van, Switala AE, Engeland H van, Heinsen H, Steinbusch HWM, Hof PR, Trippe J, Stone J, Schmitz C. (2006) Minicolumnar abnormalities in autism. *Acta Neuropathol (Berl)* 112: 287–303.
87. Courchesne E, Mouton PR, Calhoun ME, Ahrens-Barbeau C, Hallet MJ, Barnes CC, Pierce K, Semendeferi K (2013). An Overabundance of Prefrontal Cortex Neurons Underlies Early Brain Overgrowth in Autism. *Neurostereology Unbiased Stereol Neural Syst*: 73–83.
88. Chance SA, Casanova MF, Switala AE, Crow TJ Esiri MM. (2006) Minicolumn thinning in temporal lobe association cortex but not primary auditory cortex in normal human ageing. *Acta Neuropathol (Berl)* 111: 459–464.
89. Chance SA, Clover L, Cousijn H, Currah L, Pettingill R Esiri MM. (2011) Microanatomical Correlates of Cognitive Ability and Decline: Normal Ageing, MCI, and Alzheimer's Disease. *Cereb Cortex* 21: 1870–1878.
90. Courchesne E and Pierce K. (2005) Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. *Curr Opin Neurobiol* 15: 225–230.
91. Cho RY, Konecky RO, Carter CS. (2006) Impairments in frontal cortical γ synchrony and cognitive control in schizophrenia. *Proc Natl Acad Sci* 103: 19878–19883.