Aboitiz et al.'s argument that the mammalian isocortex evolved from the reptilian dorsal cortex is a tour de force that elegantly integrates comparative anatomical, developmental, genetic, paleontological, and behavioral evidence. We are neurophysiologists who study associative learning and predict impending motor action in mammals by recording simultaneously from olfactory and motor areas as they execute voluntary, skilled tasks. As such, we would like to address how the neural dynamics used by circuits including the isocortex, hippocampus, olfactory cortex, and motor areas may have concurrently evolved.

At the behavioral level, animals' actions stem from an integration of sensory cues, motivational states, and motor planning. Underpinning this integration is an intricate interplay among signal transduction, gene expression, and electrical activity within and across neurons that evolved over the course of billions of years. These biochemical and biophysical mechanisms in turn permit neurons to communicate with one another such that, at times, vast neural networks transmit information to and from one another using common rhythmic states. Our research has shown that in rodents, olfactory and motor circuits interact in a distinctive, time-locked manner just prior to the execution of a learned, olfactorily guided motor task (Hermer-Vazquez et al., in press). We believe that the dynamics allowing this integration date back to the earliest chordates such as amphioxus, which acted predominantly using olfactory cues (Holland & Holland 2001; Lacalli 2001; Satoh et al. 2002). The olfactory-motor linkage was refined in the agnathans and other early vertebrates, whose entire pallium received olfactory inputs subserving the behavioral goal of predation (cf. the target article; Lacalli 2001).

Further anatomical and physiological evidence suggests that the earliest cortically based sensory-motivational-motor linkages recruited olfactomotor dynamics. The lateral pallium of reptiles is thought to be homologous to the piriform cortex of mammals (Martinez-Garcia et al. 1986), which is considered to be an evolutionarily ancient multimodal associative area facilitating simultaneous linkages among olfactory, somatosensory, autonomic, motivational, and motor information (Johnson et al. 2000). Furthermore, the piriform cortex projects heavily to the entorhinal cortex (Johnson et al. 2000), just as the lateral cortex in reptiles (along with lemnothalamic inputs) projects heavily to the hippocampus (cf. the target article). With the evolution of cellular mechanisms permitting graded, *persistent* neural activity in the entorhinal-hippocampal complex, percepts could be *maintained* in memory (Egorov et al. 2002), facilitating the formation of associations among stimuli occurring at different points in time. Later in evolution (e.g., in primates), previously olfactory memory circuits such as those involving the perirhinal cortex came to be used for nonolfactory memory such as visual object recognition (Bussey et al. 2003; Murray & Richmond 2001).

These facts and arguments suggest that the emerging neural dynamics underlying olfactory-motor associations could have formed the basis for multimodal associations involving isocortical areas when collothalamic inputs were routed to the hippocampus. What are the hallmarks of the interlocking biochemical, biophysical, and large-scale network processes found in olfactory-motor circuits? One example that illustrates this multiscale coordination involves the frequency-dependent modulation of piriform and motor cortical activity by projections from a third brain system, the basal forebrain. Basal forebrain glutamatergic, GABAergic, and cholinergic neurons project topographically to both the piriform and motor cortices (Donoghue & Parham 1983; Manns et al. 2003; Rosin et al. 1999; Wenk et al. 1980; Woolf et al. 1984). The coordinated release of these neurotransmitters, among others, during attentive perception and recall, sculpts the patterns of activity in task-related neural circuits in part by modifying the dynamics between inhibitory and excitatory network elements (Hagevik & McClellan 1994; Poschel et al. 2002; Steriade 1997; Whittington et al. 1995). These modifications – again, among other effects – alter the coupled, transient oscillatory states seen across large networks such as the olfactomotor circuitry. There is

debate over the precise role played by subthreshold oscillations and suprathreshold oscillations, as manifested in regular inter-spike intervals, in neural coding. However, most researchers now agree that both rate coding and temporal coding, including modifications of the phase, amplitude, and frequency of oscillations, are involved in neural computations (Ahissar 1998; Mehta et al. 2002). It is also widely agreed that oscillatory states and precise spike timing are required for many forms of learning, as instantiated in changes in synaptic efficacy via long-term potentiation or depression (Bach et al. 1995; Tsien 2000; Tsodyks 2002).

Our recordings of local field potentials and spikes in the posterior piriform cortex, primary motor cortex, and subcortical motor areas of awake, behaving rats exemplify the importance of oscillatory states during learned behaviors. During olfactory recognition preceding the execution of a learned motor skill to attain an olfactory target, we have found a characteristic, transient, low-frequency oscillation occurring across the olfactory and motor areas (Hermer-Vazquez et al., in press). Concurrently, the amplitude and coherence across beta to gamma frequency bands in these task-related areas increase (Hermer-Vazquez et al., in press). A growing body of evidence indicates that the release of acetylcholine, glutamate, and GABA by the basal forebrain, in concert with dopamine release by the nigrostriatal and VTA systems, norepinephrine release by the locus coeruleus, and the release of other neuromodulators, causes this suite of changes in frequency, phase, and amplitude (Cassim et al. 2002; Lestienne et al. 1997; Manns et al. 2003; Taschenberger et al. 2002). In contrast, when the animal is not engaged in olfactory-related behaviors, the low-frequency rhythms are not synchronized across olfactory cortices and other brain areas and activity in other frequency bands, on average, is at background levels (Manns et al. 2003; Vanderwolf 1992).

This evolutionarily ancient, momentary broadband coherence on olfactory stimulus recognition appears to have been conserved in isocortical-motor circuits. For example, during a visual GO–NO GO paradigm run with monkeys, coherence among multiple high frequency bands increased at specific moments during each trial in task-related visual and motor areas (Bressler et al. 1993), similar to what we have found in olfactory and motor circuits in rodents. Transient coherence across multiple high-frequency bands has also been reported across task-related isocortical visual and somatosensory areas in humans during an associative learning task in which a color cue predicted a mild electric shock (Miltner et al. 1999). Also as in the piriform cortex, hippocampus, and M1 (Barkai & Hasselmo 1997; Hasselmo 1999; Hasselmo et al. 2002; Linster & Hasselmo 2001), acetylcholine (Hohmann & Berger-Sweeney 1998; Kilgard & Merzenich 1998; Schultz et al. 2000) plays a prominent role in attention, synaptic plasticity, and recall in all tested isocortical areas (e.g., Hohmann & Berger-Sweeney 1998; Kilgard & Merzenich 1998; Schultz et al. 2000). These observations support the hypothesis that the spatial and frequency modulations seen in ancient vertebrate olfactomotor circuits formed the biophysical basis for communication across isocortical, limbic, and motor circuits.

Reptilian cortex and mammalian neocortex early developmental homologies

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Abstract: I agree with the view expressed in the target article that the early structural organization of the mammalian neocortex (the primordial neocortical organization) is different from its final one and resembles the more primitive organization of reptilian cortex. During the early development of the neocortex, a distinctly mammalian multilayered pyramidal-cell plate is introduced within a more primitive reptilian-like cortex, establishing simultaneously layer I (marginal zone) above it and layer VII (subplate zone)

below it. This multilayered pyramidal-cell plate represents a recent mammalian innovation in the evolution of the cerebral cortex of vertebrates. Hence, the term *neocortex* is preferable to *isocortex*.

This is an excellent and well-documented article. I will comment on one aspect of it – that concerning the early developmental homologies between the reptilian cortex and the mammalian neocortex. Based on a variety of embryological, functional connectivity, neurochemical, and genetic data, the authors of the target article propose the existence of developmental homologies between some components of the reptilian cerebral cortex and those of the deeper layers of the mammalian isocortex (neocortex) and suggest a common ancestral origin for them. Their observations imply a dual organization for the mammalian neocortex with primitive reptilian-like elements in lower cortical strata and more distinctly mammalian elements throughout the upper strata. The idea of a dual developmental origin for the mammalian neocortex was first introduced in a rapid Golgi study of the early embryonic development of the cat neocortex (Marín-Padilla 1971). From a morphological perspective, the cat neocortex starts to develop, after a transient subpial (marginal) organization with horizontal neurons, with the establishment of a primordial neocortical organization (PNO), recognized today as the preplate. This PNO is characterized by superficial horizontal neurons (precursors of Cajal-Retzius cells) and by deep pyramidal-like neurons with axons that reach the subcortical white matter and Martinotti-like neurons with ascending intracortical axons. The neuronal and fiber organization of the original PNO resembles the more primitive cortical organization of reptiles. Subsequently, a cortical o, more appropriately, a pyramidal-cell plate (PP), starts to form *within* this PNO by the progressive incorporation of migrating neurons from the paraventricular germinal matrix. The appearance of the PP results in the establishment of three distinct strata in the mammalian neocortex. They include, layer I (marginal zone) with Cajal-Retzius neurons, layer VII (subplate zone) with pyramidal-like (long circuit) and Martinotti (local circuit) neurons, and an expanding pyramidal-cell plate between them, from which layers VI, V, IV, III, and II will eventually evolve (Marín-Padilla 1971; 1978; Marín-Padilla & Marín-Padilla 1982). The PP is considered to represent a recent mammalian innovation that becomes progressively incorporated into a more primitive reptilian-like cortical organization represented by layer I (external plexiform lamina) and layer VII (deep plexiform lamina) composed of and characterized by specific neuronal types and fibers systems (Marín-Padilla & Marín-Padilla 1982). Moreover, the original PNO, now represented by layers I and VII, is considered to be functionally competent during the formation of the PP, roughly, from the 25th to the 43rd day of gestation in the cat (Marín-Padilla 1971; 1972).

According to Aboitiz et al., only the deepest elements of the neocortex original preplate retain the more primitive reptilian features. The developmental history of the deep pyramidal-like neurons of the cat neocortex suggests that, prior to the functional maturation of the pyramidal neurons of the PP, they are the only source of cortical-subcortical connections (Marín-Padilla 1971; 1972). Moreover, as the pyramidal neurons of the PP begin to mature functionally (around the 45th day of gestation, in the cat), the deep neurons of the subplate undergo significant developmental transformations, losing their original functional contacts with layer I and assuming the morphological feature of polymorphous neurons (Marín-Padilla 1972). On the other hand, the Cajal-Retzius cells of the original PNO (preplate) assume new and important roles in the development of the mammalian neocortex (Marín-Padilla 1990; 1992). By attracting migratory neurons toward layer I and establishing early functional contacts with their terminal dendritic bouquets, the Cajal-Retzius neuron plays a significant role in the formation of the mammalian neocortex, particularly of its pyramidal-cell plate (Marín-Padilla 1992). Both the unique morphology of the mammalian pyramidal neuron and its stratified inside-outside cortical placement are also developmental processes that depend on these neurons (Marín-Padilla 1992; 1989).

The recent discovery of REELIN has corroborated most of the developmental roles attributed to the Cajal-Retzius neurons by these original morphological Golgi studies.

These early morphological Golgi studies support the ideas proposed in this target article. The distinctly mammalian multilayered pyramidal-cell plate represents a recent innovation which is introduced and progressively expands within a more primitive cortical organization that has features resembling those of the reptilian cortex. This primitive cortical organization may be functionally competent during the early embryonic life of mammals. Moreover, the basic body musculature of a mammalian young embryo is more reptilian-like than mammalian and should require a more primitive cortical control. The competence of the Golgi method in demonstrating the structural and, at times, the functional organization of the nervous system is acknowledged and its use is encouraged.

The origin of the amniote sensory and motor cortices

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Abstract: A rigorous cladistic analysis of the dorsal pallium of amniotes indicates that the stem amniote lacked sensorimotor areas. Reptiles apparently acquired a visual cortex by parcellation from the multimodal, hippocampal-like mediodorsal pallium of stem amniotes. The high number of sensory areas of the mammalian isocortex might derive from the specific properties it shows, such as growth-promoting influence on thalamic axons.

In their insightful target article, Aboitiz and collaborators assume the viewpoint that the sensorimotor cortices of all extant amniotes are homologous (Medina & Reiner 2000). If so, the mammalian isocortex would have been generated in two steps. First, the dorsal pallium of stem amniotes acquired sensory inputs from the dorsal thalamus (and descending motor projections). Second, in synapsids this pre-isocortex acquired new developmental mechanisms resulting in a six-layered architecture. In this commentary, I reconsider the evolution of the sensori(motor) cortex of amniotes and discuss its implications in the origin of the isocortex.

Whereas the Wulst of birds includes a somatomotor area (Wild 1992; Wild & Williams 2000), neither lizards (Bruce & Butler 1984a; Lohman & Van Woerden-Verkley 1978; Neary & Wilczynski 1977) nor turtles (Hall & Ebner 1970) show somatosensory thalamic projections to the cortex. Using the rudimentary methodology available at that time, Johnston (1916) reported movements elicited by electric stimulation of the rostral dorsal cortex in reptiles, but his results were never replicated. Indeed, lizards possess neither corticorubral pathways (Martinez-Marcos et al. 1999) nor cortical projections to other premotor centres (Hoogland & Vermeulen-Vanderzee 1989). Hence, the available evidence does not support the presence of a somatomotor cortex in extant reptiles.

Like the avian Wulst (Karten et al. 1973), the dorsal cortex (DC) of turtles displays a visual area that includes the pallial thickening (PT), which receives a projection from the dorsal lateral geniculate nucleus of the thalamus (GLd; Hall & Ebner 1970). In lizards this projection reaches just the pallial thickening (Kenigfest et al. 1997; Lohman & Van Woerden-Verkley 1978). Despite the lack of data in crocodiles, it is generally accepted that all sauropsids have a dorsal visual cortex. However, the avian and reptilian visual cortex is located in the rostral dorsal pallium, whereas in all mammals it is found in the caudal (iso)cortex (Kaas 1980; Krubitzer 1995). Just as the mediolateral topography of the pallium is fundamental to establish phylogenetic relationships among cortical structures, so too is the rostrocaudal topography, as the expression of ho-