Chapter 5
Evoked and Induced Gamma-Frequency Oscillations in Autism

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5.1 Minicolumnar Neuropathology Model of Autism and EEG Gamma

Recent studies by our group have characterized the neuropathology of autism as that of a minicolumnopathy. Postmortem studies using computerized image analysis of pyramidal cell arrays have found that the brains of autistic individuals have smaller minicolumns with most of the decrease stemming from a reduction in its peripheral

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neuropil space, with little, if any reduction, in their core space. This finding has been reproduced using different techniques (e.g., GLI) and independent populations (Casanova et al. 2002a, b, c, 2006a, b). It is now known that minicolumnar width reduction in autism spans supragranular, granular, and infragranular layers (Casanova et al. 2010). The most parsimonious explanation for the findings is the possible abnormality of an anatomical element in common to all layers. The peripheral neuropil space of minicolumns provides, among other things, for inhibitory elements distributed throughout all of its laminae. This is the so-called shower curtain of inhibition of the minicolumn described by Szentágothai and Arbib (1975). Our findings therefore suggest a deficit within the inhibitory elements that surround the cell minicolumn (Casanova et al. 2006a).

The anatomical disposition of inhibitory elements within the shower curtain of inhibition provides clues as to their function. While tangentially arrayed basket cells function, in part, to coordinate activity among remote neuronal ensembles, by contrast, radially oriented inhibitory interneurons prominently located in the peripheral neuropil space surrounding pyramidal cell columns likely function to segregate columns from interference, both from other minicolumns within an array and from fields of activity or inhibition in neighboring minicolumnar arrays (Casanova et al. 2003). The finding suggests a mechanistic explanation to the inhibitory/excitatory imbalance in autism and a possible explanation to the multifocal seizures often observed in this condition (Casanova et al. 2003).

Oscillations of pyramidal cells in minicolumns and across assemblies of minicolumns are maintained by networks of different species of inhibitory, GABA-expressing interneurons. In this regard interneurons make a critical contribution to the generation of network oscillations and help synchronize the activity of pyramidal cells during transient brain states (Mann and Paulsen 2007). Local excitatory–inhibitory interactions help shape neuronal representations of sensory, motor, and cognitive variables and produce local gamma-band oscillations in 30–80 Hz range (Donner and Siegel 2011). The excitatory–inhibitory bias caused by faulty pyramidal cell-interneuronal dyads provides a receptive scenario to gamma-frequency abnormalities in autism.

Gamma frequencies are closely associated with sensory processing, working memory, attention, and many other cognitive domains (Ward 2003; Jensen et al. 2007). The brain's limited long-range wiring cannot directly sustain coordinated activity across arbitrary cortical locations, but it can convey patterns of synchronous activity as oscillatory neuronal fluxes, represented by local field potentials measured by EEG. Coordination of oscillations at varying interacting frequencies allows for relatively efficient and unconstrained segregation in varying forms and across hierarchical cortical levels. Disrupted patterns of coordinated oscillatory output in distributed minicolumnar networks might be associated with cortical "disconnection" in autism. More specifically, altered oscillatory activity in developing cortical circuits may contribute to impaired development of intra-areal and transcortical connections giving rise to a bias in short (e.g., arcuate) vs. long corticocortical projections (e.g., commissural fibers) (Casanova et al. 2006a, b, 2009). The pervasive nature of abnormalities ingrained in this oscillatory activity bears significant

analogy to the cognitive deficits observed in autism. It is therefore unsurprising that gamma oscillations have been claimed to be directly related to the pathophysiology of autism (Sohal 2012). To the authors' knowledge every study on gamma frequencies in autism has been abnormal.

5.2 Functional Significance of Gamma Oscillations

Electroencephalography (EEG) has been used to decompose oscillatory patterns into several frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–80 Hz), each of which operates over various spatiotemporal scales to control cortical activity. High-frequency gamma-band oscillations are most directly associated with entrainment of local networks. Strong evidence indicates that this gamma-frequency activity is associated with binding of perceptual features in animals (Herrmann and Knight 2001). Human experiments have also found that induced gamma activity correlates with binding (Kaiser 2003). Binding of widely distributed cell assemblies by synchronization of their gamma-frequency activity is thought to underlie cohesive stimulus representation in the human brain (Keil et al. 1999; Rodriguez et al. 1999; von Stein et al. 1999; Bertrand and Tallon-Baudry 2000; Kahana 2006; Pavlova et al. 2006). Increased gamma activity has been most widely associated with top-down attentional processing and object perception (Rodriguez et al. 1999; Gruber et al. 2001; Fell et al. 2003; Nakatani et al. 2005) subserving Gestalt pattern perception (von Stein et al. 1999; Herrmann and Mecklinger 2000).

Contemporary models of neural connectivity outline the role of integration and segregation of both local and distal networks, their phase synchronization and large-scale integration of evoked and induced neural activity (Tallon-Baudry et al. 1998, 2005; Varela et al. 2001; Tallon-Baudry 2003). Functional coupling and decoupling of neural assemblies could be analyzed within specific time and frequency windows of electrocortical activity. Gamma-band activity can be divided into either evoked or induced: evoked gamma-band activity has been identified at a latency of around 100 ms after stimulus onset (Bertrand and Tallon-Baudry 2000; Herrmann and Mecklinger 2000) and is phase-locked to the onset of the stimulus; induced gamma-band activity occurs later with a variable onset although it has been reported to start at around 250 ms (Brown et al. 2005) (Fig. 5.1). It has been proposed that evoked gamma-band activity reflects the early sensory processing and the binding of perceptual information within the same cortical area (i.e., intra-areal), whereas induced gamma-band activity reflects the binding of feed-forward and feedback processing in a whole network of cortical areas (corticocortical) (Shibata et al. 1999; Müller et al. 2000; Brown et al. 2005). Variations of such activity have been termed event-related synchronization and desynchronization (ERS/ERD) (Pfurtscheller and Aranibar 1977) or event-related spectral perturbations (ERSP) (Makeig et al. 2004) and have been associated with the activation of task-relevant neuronal assemblies (Pfurtscheller and Lopes da Silva 1999; Rippon et al. 2007).

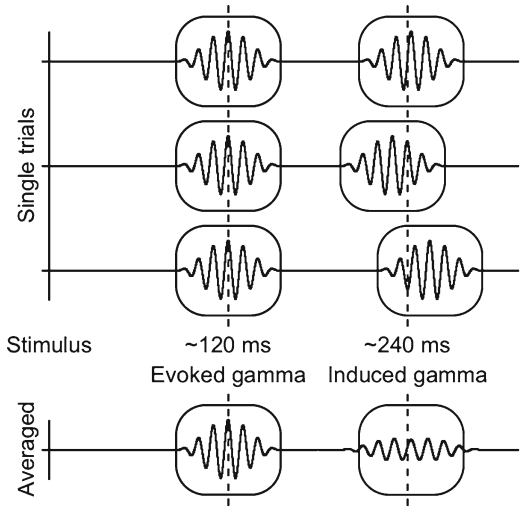

Fig. 5.1 Schematic representation of early evoked (peaking around 120 ms poststimulus) and late induced gamma (peaking around 240 ms) oscillations in single trials and averaged gamma response during visual oddball task

5.3 Abnormalities of Gamma Activity in Autism

Excitatory output of projection neurons is modulated and coordinated by oscillatory electrocortical activity of area-specific arrays of inhibitory interneurons. Phasic synchronization of these local oscillation patterns may provide a basis for functional integration across widely distributed cortical networks (Müller et al. 2000; Varela et al. 2001; Tallon-Baudry 2003, 2005). Visual and auditory perception anomalies, as well as some features of language processing and social communication deficits, and executive dysfunctions associated with "weak central coherence" in autism (Frith and Happé 1994; Morgan et al. 2003; Mottron et al. 2003; Plaisted et al. 2003; Happé and Frith 2006) may be attributed to reduced gamma-frequency synchronization and decreased temporal binding of activity between networks processing local features.

Disrupted visual perceptual congruence in individuals with autism is illustrated by a study (Brown 2005) in which subjects were presented with a visual-shape illusion (Kanizsa 1976). The autistic individuals exhibited a burst of gamma activity in posterior areas at 300 ms, which was greater in power and duration than the corresponding gamma response in controls. In another study Brown et al. (2005) could not find reaction time or accuracy differences between groups in a task of Kanizsa figure identification, but they showed significant task-related differences in gamma activity. Control participants showed typical gamma-band activity over parietal regions at around 350 ms, while autistic participants showed overall increased activity, including an early 100 ms gamma peak and a late induced peak, occurring earlier than that shown by the control group. The authors interpreted the abnormal gamma activity to reflect decreased "signal to noise" due to decreased inhibitory processing. Brock et al. (2002) described the parallels between the psychological

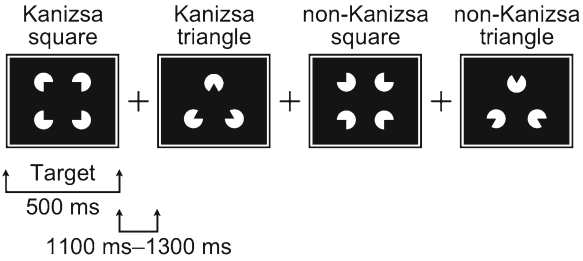

Fig. 5.2 Kanizsa and non-Kanizsa figures were used as stimulus materials in this experiment. In particular, the stimulus types used in the experiment are Kanizsa *square* (target), Kanizsa *triangle*, non-Kanizsa *square*, and non-Kanizsa *triangle*. The nontarget Kanizsa *triangle* was introduced for the differentiation of processing Kanizsa figures and targets. The stimuli consisted of either three or four inducer disks which are considered the shape feature and either do or do not constitute an illusory figure (*square*, *triangle*). Kanizsa illusory figures readily induce gamma response during perceptual processing (Herrmann and Mecklinger 2001; Brown 2005)

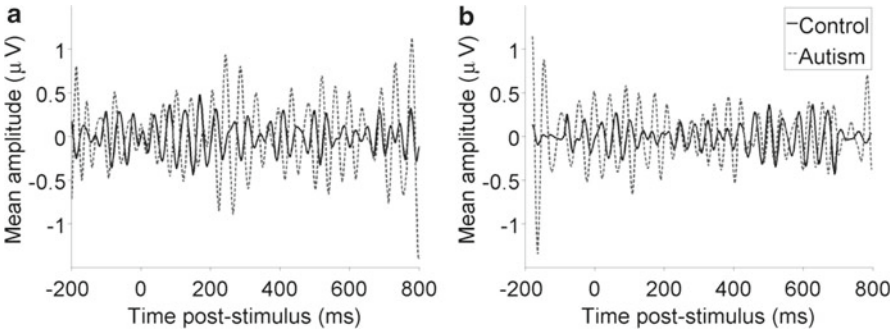

Fig. 5.3 Gamma-frequency oscillations in response to Kanizsa target (**a**) and nontarget (**b**) stimuli. Children with autism show higher power of late (240–400 ms poststimulus) gamma oscillations in response to the target Kanizsa stimulus and higher power of early (40–180 ms poststimulus) gamma oscillations in response to the nontarget Kanizsa stimulus

model of "central coherence" in information processing (Frith and Happé 1994) and the neuroscience model of neural integration or "temporal binding." They proposed that autism is associated with abnormalities of information integration that is caused by a reduction in the connectivity between specialized local neural networks in the brain and possible over-connectivity within the isolated individual neural assemblies. This concept was further elaborated in an "impaired connectivity" hypothesis of autism (Rippon et al. 2007), which summarized theoretical and empirical advances in research implicating disordered connectivity in autism. The authors highlighted recent developments in the analysis of the temporal binding of information and the relevance of gamma activity to current models of structural and effective connectivity based on the balance between excitatory and inhibitory cortical activity (Casanova et al. 2002a, b, c; Rubenstein and Merzenich 2003; Belmonte et al. 2004a, b) (Figs. 5.2 and 5.3).

It has been proposed that "weak central coherence" (Frith and Happé 1994; Morgan et al. 2003; Mottron et al. 2003; Plaisted et al. 2003; Happé and Frith 2006; Murias et al. 2007) in autism could result from a reduction in the integration of specialized local networks in the brain caused by a deficit in temporal binding (Brock et al. 2002; Rippon et al. 2007). Audiovisual perception anomalies associated with weak central coherence may be attributed to a reduction in synchronization of gamma activity between networks processing local features and can explain some of the features of language deficits, executive dysfunctions, and other impairments in social communication in autism. Excessive but not synchronized gamma can be linked to a reduction in the ability to focus attention. In autism, uninhibited gamma activity suggests that none of the circuits in the brain can come to dominance because too many of them are active simultaneously (Brown et al. 2005). A proposed "temporal binding deficit" hypothesis of autism (Grice et al. 2001; Brock et al. 2002; Rippon et al. 2007) suggests that many features of autism, such as superiority in processing of detail (local processing) and disadvantage in global processing, necessitating integration of information either over space, time, or context, can be explained by a failure of binding between cortical areas. Abnormal gamma activation would suggest disrupted neural signaling and would support the hypothesis of abnormal regional activation patterns.

5.4 Investigation of Evoked and Induced Gamma Responses in Autism

It is well known that networks of inhibitory interneurons acting as GABA-gated pacemakers are critically involved in gamma oscillations (Grothe and Klump 2000; Whittington et al. 2000). Electrophysiological research has provided evidence that gamma activity is a physiological indicator of the co-activation of cortical cells engaged in processing visual stimuli (Singer and Gray 1995; Tallon-Baudry and Bertrand 1999; Keil et al. 2001) and integrating different features of a stimulus (Müller et al. 2000). The onset of a visual stimulus gives rise to a burst of gamma activity over occipital sites, and when more complex tasks are undertaken, discrete bursts of gamma activity have been identified overlying cortical regions thought to be engaged in those tasks (Brown et al. 2005). For example, tasks involving attention modulation or the top-down integration of features give rise to simultaneous bursts of gamma over frontal and occipitoparietal regions (Rodriguez et al. 1999; Müller et al. 2000; Müller and Gruber 2001).

Kanizsa illusory figures (Kanizsa 1976) have been shown to produce gamma oscillation bursts during visual cognitive tasks (Tallon-Baudry et al. 1996; Herrmann et al. 1999). Kanizsa stimuli consist of inducer disks of a shape feature and either constitute an illusory figure (square, triangle) or not (colinearity feature); in non-impaired individuals, gamma activity has been shown to increase during "target-present" compared to "target-absent" trials (Müller et al. 1996; Tallon-Baudry et al. 1996; Brown et al. 2005). In several studies, Kanizsa figures were employed as stimuli in an oddball task paradigm to investigate effects of target classification and

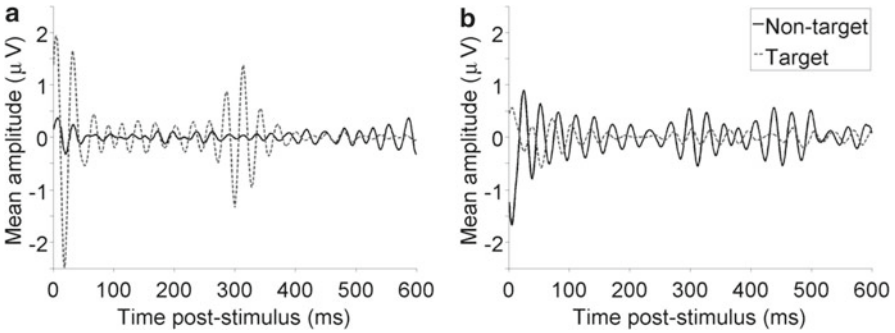

Fig. 5.4 Frontal (F1) induced gamma responses (peak of oscillations close to 300 ms) in children with autism spectrum disorder (ASD, $N = 15$) and age-matched controls ($N = 15$) in Kanizsa oddball task. The control group (**a**) shows higher amplitude of gamma burst to target stimuli, while the ASD group (**b**) shows higher gamma response to nontarget Kanizsa figures

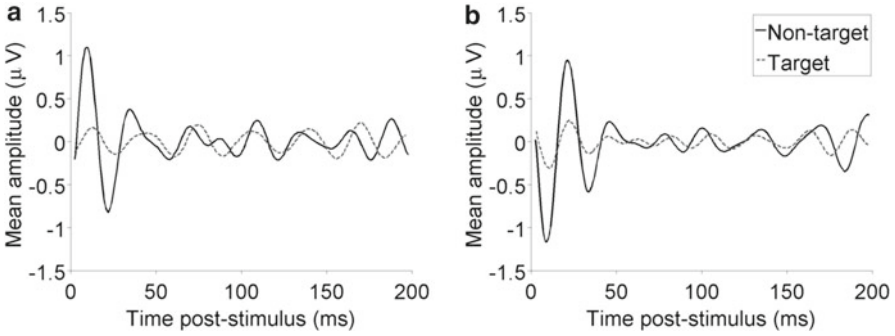

Fig. 5.5 Early evoked gamma oscillations to target and nontarget rare Kanizsa figures at the *left* lateral frontal site F7 (**a**) and parietal site P7 (**b**) in a group of children with autism. Evoked gamma to nontarget stimuli is comparable and even larger in amplitude than gamma response to target stimuli

discrimination between illusory stimulus features (Tallon-Baudry et al. 1998; Herrmann and Mecklinger 2000; Böttger et al. 2002; Brown 2005; Sokhadze et al. 2009a). In our study of gamma activity in autism (Sokhadze et al. 2009a; Baruth et al. 2010; Casanova et al. 2012), we used a modification of such oddball test where subjects performed a visual discrimination task which required a response to target Kanizsa squares among nontarget Kanizsa triangles and non-Kanizsa figures. This task was used to examine gamma-band EEG activity and event-related potentials (ERP). Power of induced gamma oscillations (at twelve left and right frontal, central, parietal, and occipital EEG sites, 30–80 Hz range, in μV^2) was analyzed using wavelet transformation. Density of induced power of gamma oscillations ($\mu V^2/Hz$) and power density difference between gamma response to nontarget and target Kanizsa stimuli (target minus nontarget Kanizsa conditions) were also calculated and analyzed. Power of gamma oscillations in response to nontarget Kanizsa and non-Kanizsa standard stimuli was higher in autism group at the left frontal (F1, F7), left and right parietal (P1, P2, P7, P8), and occipital (O1, O2) EEG channels (Figs. 5.4 and 5.5).

Group (control, autism) differences in gamma oscillation power to nontarget and target Kanizsa stimuli were better expressed over the lateral frontal (F7, F8) and parietal (P7, P8) EEG sites. A *Stimulus* (target, nontarget) × *Group* (autism, control) interaction was highly significant for all recording sites ($p < 0.001$) and described as higher gamma power to nontargets in autism group compared to controls. We found also a *Hemisphere* × *Group* interaction across the lateral frontal and parietal sites, with difference between target and nontarget stimuli being more negative in autism group at the right hemisphere. Most consistent finding was that gamma induced by the nontarget stimuli was globally higher in autistic subjects compared to controls at all sites. This interaction for *Stimulus* (nontarget, target) × *Topography* (frontal, parietal) × *Group* (autism, control) was significant. Power density differences to target and nontarget stimuli revealed significant and reproducible effect of higher response to nontargets rather than target Kanizsa figures in the autism group (Sokhadze et al. 2009a).

Our findings of higher amplitude of ERP components (Sokhadze et al. 2009a, b; Casanova et al. 2012) and excessive gamma oscillations (Sokhadze et al. 2009a; Baruth et al. 2010, 2011) in response to nontarget items are in agreement with other studies noting that neural systems in the brain of autistic patients are often inappropriately activated (Belmonte and Yurgelun-Todd 2003a). Kemner et al. (1994) also reported that the visual N200 ERP component to novel distracters is larger when a person with autism is performing a task even when these novel stimuli are not relevant to the task in question. According to Belmonte and Yurgelun-Todd (2003a, b), perceptual filtering in autism occurs in an all-or-none manner with little specificity for the task relevance of the stimulus. Perceptual filtering may primarily depend on the control of general arousal rather than the activation of specific perceptual system. Since in many tasks requiring attention, persons with autism perform at close to normal levels despite generally high arousal and low selectivity, some compensatory mechanisms may operate at a higher stage of processing to sort out relevant stimuli from poorly discriminated background. One candidate mechanism was suggested as an active inhibition of irrelevant distracters that have passed through earlier filtering (Belmonte and Yurgelun-Todd 2003b). It is unsurprising that increased ratio of excitation/inhibition in key neural systems and high "cortical noise" have been considered as a core abnormality of autism (Casanova et al. 2003; Rubenstein and Merzenich 2003).

Our study showed very similar gamma activation pattern both to "target" and "nontarget" Kanizsa stimuli (Sokhadze et al. 2009a; Baruth et al. 2010, 2011). Furthermore, dipole source coherence analysis (Hoechstetter et al. 2004) of early evoked (40–150 ms) 40 Hz centered gamma responses to targets at the parietal sites (P3, P4) showed between three groups differences, specifically, higher hemispheric coherence coefficient values in attention deficit/hyperactivity disorder (ADHD) as compared to autism group (0.59 in ADHD vs. 0.38 in autism, $p = 0.003$).

The gamma frequencies, particularly those centered about 40 Hz, have been tied to visual, attentional, cognitive, and memory processes (Başar et al. 2001). As it was mentioned above, following a stimulus presentation during visual task, two gamma oscillations are typically noted: an early evoked oscillation and a late induced

oscillation (Başar et al. 2001). The evoked gamma oscillations typically occur within the first 100 ms after the onset of a stimulus and are locked in time from trial to trial. Because little variation is seen in the latency of the evoked gamma with changing stimulus type, it is believed that it may be a result of sensory processes. Conversely, induced gamma oscillations occur later, after 240 ms poststimulus, and vary in latency from trial to trial (Tallon-Baudry and Bertrand 1999). These variations occurring in time window typical for P300 ERP component may suggest that the induced gamma oscillations are related to higher cognitive processes (Tallon-Baudry 2003). Deviations from typical gamma-band activity have been reported in several studies on neurological disorders, including epilepsy, Alzheimer's disease, ADHD, and autism (Herrmann and Demiralp 2005).

Our study (Baruth et al. 2010) indicated that individuals with autism had a minimal difference in evoked gamma power between target and nontarget Kanizsa stimuli at all EEG channels of interest. In fact, evoked gamma power responses were slightly larger in response to nontarget Kanizsa stimuli relative to targets. In contrast the control group had a significantly higher evoked gamma power to target Kanizsa stimuli compared to nontarget Kanizsa stimuli showing clear differences in visual stimulus discrimination. Additionally, the control group showed a greater difference in evoked gamma power between frontal and parietal regions to all stimuli over the left hemisphere: controls had more frontal as compared to parietal gamma activity, while the autism spectrum disorder (ASD) group showed negligible topographic differences. These findings are similar to the findings of Grice et al. (2001) where individuals with autism did not show significant differences in frontal gamma activity during the processing of upright and inverted faces, whereas control subjects showed clear discriminative increases in frontal gamma activity when the faces were presented upright vs. inverted. These findings also correspond to our previous investigation (Sokhadze et al. 2009a) where we found positive differences in gamma oscillation power (i.e., 30–80 Hz, 0–800 ms poststimulus) between target and nontarget Kanizsa stimuli where it decreased, especially over the lateral frontal (F7, F8) and parietal (P7, P8) EEG sites, in adolescents and young adults with ASDs; this was mainly due to significant increases in gamma power at all recording sites, especially evoked gamma (i.e., ~100 ms) over frontal channels, to nontarget Kanizsa stimuli compared to controls. Our results indicate that in ASD evoked gamma activity is not discriminative of stimulus type, whereas in controls early gamma power differences between target and nontarget stimuli are highly significant.

There are a few plausible explanations as to why the gamma response does not allow for discrimination between stimuli in ASD. It is well known that ASD is associated with amplified responses to incoming sensory information. Studies suggest that the neural systems of individuals with ASD are over-activated (Belmonte et al. 2004a, b) and there is a lack of cortical inhibitory tone (Casanova et al. 2002a, b, 2006a; Rubenstein and Merzenich 2003). In a network that is over-activated and "noisy," local cortical connectivity may be enhanced at the expense of long-range cortical connections, and individuals with ASD may have difficulty directing attention. It may not be possible for them to selectively activate specific perceptual systems based on the relevance of a stimulus (i.e., target vs. nontarget).

Our previous findings investigating ERP during a visual novelty processing task further support the idea of difficulty discriminating task-relevant from irrelevant stimuli in ASD (Sokhadze et al. 2009b). Briefly, we found that subjects with ASD showed a lack of stimulus discrimination between target and nontarget stimuli compared to controls, and this was mainly due to significantly prolonged and augmented ERP components to irrelevant distracter stimuli over frontal and parietal recording sites. Early ERP components (e.g., P100, N100) were especially increased to irrelevant distracter stimuli in the ASD group indicating augmented responses at early stages of visual processing (i.e., ~100 ms). Early gamma components (i.e., evoked) are measured at the same time over the same cortical regions as these early ERP components. The very early burst of gamma activity between 80 and 120 ms found by Brown et al. (2005) and our findings of augmented evoked gamma (Sokhadze et al. 2009a) and early ERP responses (Sokhadze et al. 2009b) to task-irrelevant stimuli support the idea of disturbances in the activation task-relevant neuronal assemblies and the perceptual control of attention in ASD. Although we found significant group differences in relative evoked gamma power in processing relevant and irrelevant visual stimuli in this study, it is important to mention why we did not find significantly amplified relative evoked gamma power in the ASD group compared to controls. We attribute this to the fact that relative gamma-band power is calculated in reference to the entire EEG spectrum, and in ASD it has previously been shown that other frequency ranges are augmented as well (Dawson et al. 1995; Stroganova et al. 2007).

5.5 Language and Gamma Power and Coherence

Understanding of language requires integration of input of the different parts of information that are processed in different brain areas. It has been suggested that binding between different distributed parts of language processing neural network is implemented by synchronization and desynchronization of oscillatory neural activity (Singer 1999; Weiss and Müller 2003; Hald et al. 2006). Analysis of event-related changes in either power or phase coherence of EEG oscillations provides a window onto the processes of synchronization and desynchronization of neuronal populations (Tallon-Baudry and Bertrand 1999; Varela et al. 2001). Increased power and higher phase coherence between EEG recording sites is thought to reflect synchrony of activation and higher spatial co-activation of distributed neural systems that may reflect the transient formation of functional networks involved in language processing (Varela et al. 2001; Bastiaansen and Hagoort 2003; Penolazzi et al. 2009). For a proper analysis of oscillatory dynamics, one of the most analytic tools used is wavelet-based time-frequency analysis to quantify amplitude/power changes and/or event-related coherence analysis for quantifying changes in phase coherence between EEG electrodes or between dipole sources (Hoechstetter et al. 2004). Recent studies employing such techniques have clearly demonstrated that synchronous oscillations have functional significance during the execution of tasks

engaging a variety of cognitive operations, such as memory encoding and retrieval (Fell et al. 2001; Burgess and Ali 2002), working memory (Kahana et al. 1999; Jensen and Tesche 2002), face perception (Rodriguez et al. 1999), object detection (Tallon-Baudry and Bertrand 1999), and attentional processes (Klimesch 1999; Bastiaansen and Brunia 2001; Fries et al. 2001).

Recently, such studies are also being performed in the domain of language comprehension (Weiss and Rappelsberger 1996, 2000; Pulvermüller et al. 1999; Weiss et al. 2001; Bastiaansen et al. 2002a, b, 2005; Schack et al. 2003; Weiss and Müller 2003). Still, relatively little is known about synchronous oscillations and their possible functions during language comprehension. During the speech comprehension, different parts of the language processing system, such as auditory perception, phonological, morphological, syntactic, semantic, pragmatic, and prosodic analyses, have to be integrated in order to understand the meaning of the spoken sentences and to initiate appropriate response behavior. Large-scale synchronization seems particularly important with respect to distributed neuronal assemblies, which have to be integrated during complex cognitive processing (Bressler and Kelso 2001; Varela et al. 2001; Herrmann et al. 2004) and especially during language processing (Weiss and Rappelsberger 1996; Petsche and Etlinger 1998). In a study by Benasich et al. (2008), EEG gamma power was associated with attention measures in infants. A group of children with a family history of language impairment and thus at higher risk for language disorders showed consistently lower gamma over frontal regions than the well-matched controls with no such family history. The authors suggested that the emergence of high-frequency neural synchrony may be critical for cognitive and linguistic development, and children at risk for language impairments may lag in this process (Benasich et al. 2008). Further systematic studies on EEG coherence and language will elucidate and clarify the meaning and interpretation of previous findings linking EEG gamma and language.

5.6 Conclusions

Recently, there were several attempts at deriving an overarching metatheory of autism that have focused on a basic abnormality of neural connectivity (Belmonte et al. 2004a, b). This model is empirically based on lack of coordinated brain activity and abnormal "binding" in the brains of autistic patients that can be detected with EEG methodology, specifically using gamma oscillations (Brock et al. 2002; Brown 2005; Rippon et al. 2007). According to Baron-Cohen and Belmonte (2005), the combination of local sensory hyperarousal and low-level over-processing of incoming sensory stimuli concurrent with abnormalities of attention selectivity and focus may be a consequence of the over-connected low-level processing neural networks in ASDs. In such over-wired networks, signal is insufficiently differentiated from noise or task-irrelevant information, and as a result, information capacity is drastically reduced (Rubenstein and Merzenich 2003; Belmonte et al. 2004a, b; Casanova 2006). Higher-than-normal noise in cortical processes also affects normal

development of differentiated representations, because cortical response selectivity in space and time is a product of balanced inhibitory and excitatory processes. Such overrepresentation by non-differentiated systems could plausibly account, for example, for the strong aversive reactions to auditory, tactile, and visual stimuli that are commonly recorded in autistic individuals. The abnormal long-range neural connectivity model is suggested to explain deficits in high-level complex information processing functions where rapid and integrated operation of many separate neural systems is required (Minshew et al. 1997; Welchew et al. 2005). In the autistic brain, high local connectivity may develop along with deficient long-range connectivity.

In recent years, neuropathological studies of autism have revealed abnormalities in several brain regions. Changes in brain size with widespread increases in both gray and white matter volumes suggest that the underlying pathology in autism consists of widely distributed histological abnormalities. The available neuropathological and structural imaging data suggest that autism is the result of a developmental lesion capable of affecting normal brain growth. One possible explanation for this is the recent finding of minicolumnar abnormalities in autism, in particular demonstration of minicolumns of reduced size and increased number in the autistic brain (Casanova et al. 2002a, b, 2006a, b). The increased number of minicolumns reported in autism suggests a possible disruption during the earlier stages of neurodevelopment in the brain of an autistic patient. Furthermore, a minicolumnar abnormality may translate difficulties in the integration of information into a delay in language acquisition. In all, minicolumnar abnormalities may incapacitate a patient as a social being by distorting elements of the child's biopsychological experience.

The modular arrangement of the cortex is based on the cell minicolumn: a self-contained ecosystem of neurons and their afferent, efferent, and interneuronal connections (Mountcastle 2003). Our preliminary studies indicate that minicolumns in the brains of autistic patients are narrower, with an altered internal organization (Casanova 2006). More specifically, their minicolumns reveal less space for inhibitory local circuit projections. A defect in these GABAergic fibers may correlate with the increased prevalence of seizures among autistic patients. Based on the descriptions given thus far, it is possible to propose a disruption of the normal balance between excitation and inhibition in the columnar organization of autistic patients. In this regard, a series of noteworthy studies report that both children and adults with autism were superior to a control group in their ability to discriminate novel, highly similar stimuli (Plaisted et al. 2003). Autistic children also have a superior ability in discriminating display items in visual search tasks; such enhanced discrimination in autism results from low-level perceptual processing of incoming stimuli, and this is called the bottom-up approach.

Analysis of high-frequency EEG oscillations in patients with autism may provide additional information about potential neural deficits in autism. Abnormalities in these mechanisms have been associated with binding problems (the co-activation of neural assemblies), which may be present in both autism and schizophrenia (Grice et al. 2001; Brock et al. 2002). Oscillatory activity in the gamma band of the EEG has been related to Gestalt perception and to cognitive functions such as attention, learning, and memory (Kaiser 2003). Electrophysiological studies show strong

evidence that synchronized cortical activity in the gamma-frequency range could be a correlate of feature binding to form a single coherent percept. Binding of widely distributed cell assemblies by synchronization of their gamma-frequency activity is thought to underlie cohesive stimulus representation in the human brain (Kahana 2006). According to this assumption, changes in gamma EEG activity have been considered indicators of processing of Gestalt-like patterns (von Stein et al. 1999; Herrmann and Mecklinger 2000, 2001).

The "weak central coherence" (Frith and Happé 1994) in autism could result from a reduction in the integration of specialized local networks in the brain caused by a deficit in temporal binding (Brock et al. 2002). Visual and auditory perception anomalies may be attributed to a reduced coherence and synchrony of gamma activity between networks processing local features and thus explain some of the language deficits, executive dysfunctions, and other impairments in social communication in autism. The inability to reduce gamma activity according to Brown (2005) would lead to the inability to decide which event requires attention when there are multiple choices. Excessive gamma can therefore be linked to a reduction in the ability to focus attention. The "temporal binding deficit" hypothesis of autism (Brock et al. 2002; Rippon et al. 2007) suggests that many features of autism, such as superiority in processing detail (local processing) and disadvantages in global processing, can be explained by a failure of binding between cortical areas. Analysis of evoked and induced EEG gamma oscillation can therefore significantly contribute to understanding the neurobiological nature of core autism symptoms and definitely warrant further rigorous investigations.

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Biography

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Joshua Baruth graduated from the Department of Anatomical Sciences and Neurobiology at the University of Louisville School of Medicine. Joshua's research has focused primarily on the treatment of autism spectrum disorders with transcranial magnetic stimulation. He received his B.A. in classical languages and premedicine from the University of Kansas in 2005 and his master's degree in anatomical sciences and neurobiology from the University of Louisville in 2009 and his PhD in 2010. He is currently at Mayo Clinic in Minnesota as a postdoc fellow.

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Estate M. Sokhadze received a Ph.D. in human physiology in 1988 (Novosibirsk, Russia). He completed a postdoctoral fellowship in psychopharmacology at Wake Forest University in 2001–2003 and postdoctoral training in cognitive neuroscience at Rice University in 2004. Currently, Dr. Sokhadze is an associate professor of Psychiatry and Behavioral Sciences at the University of Louisville and is a director of the Evoked Potential Lab at Cognitive Neuroscience Labs. His research interests include application of dense-array EEG/ERP brain mapping, neurofeedback, TMS, and other applied psychophysiological techniques in psychiatric research. Specific psychopathology areas of interest are substance abuse, PTSD, autism, ADHD, conversion disorder, bipolar disorder, and comorbid mental conditions. He has more than 25 years of experience in applied psychophysiology and clinical neurosciences.