MISSING LINKS: THE ROLE OF PHASE SYNCHRONOUS GAMMA OSCILLATIONS IN NORMAL COGNITION AND THEIR DYSFUNCTION IN SCHIZOPHRENIA

Albert R. Haig

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Department of Psychological Medicine

University of Sydney

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SUMMARY

Introduction: There has recently been a great deal of interest in the role of synchronous high-frequency "gamma" oscillations in brain function. This interest has been motivated by an increasing body of evidence, that oscillations which are synchronous in phase across separated neuronal populations, may represent an important mechanism by which the brain binds or integrates spatially distributed processing activity which is related to the same object.

Many models of schizophrenia suggest an impairment in the integration of brain processing, such as a "loosening of associations", "disconnection", defective "multiple constraint organization", or "cognitive dysmetria". This has led to recent speculation that abnormalities of high-frequency "gamma" synchronization may reflect a core dimension of the disturbance underlying this disorder. However, examination of the phase synchronization of gamma oscillations in patients with schizophrenia has never been previously undertaken.

Method: In this thesis a new method of analysis of gamma synchrony was introduced, which enables the phase relationships of oscillations in a specific frequency band to be examined across multiple scalp sites as a function of time. This enabled, for the first time, the phase synchronization of gamma oscillations across widespread regions, to be studied in electrical brain activity measured at the scalp in humans. Gamma synchrony responses were studied in electroencephalographic (EEG) data acquired during a commonly employed conventional auditory oddball paradigm.

The research consisted of two sets of experiments. In the first set of experiments, data from 100 normal subjects, consisting of 10 males and 10 females in each age decade from 20 to 70, was examined. These experiments were designed to characterize the gamma synchronizations that occurred in response to target and background stimuli and their functional significance in normal brain activity, and to exclude the possibility of these findings being due to electromyogram (EMG) or volume conduction artifact. The
examination of functional significance involved the development of an additional new analysis technique. In the second set of experiments, data acquired from 35 patients with schizophrenia and 35 matched normal controls was analyzed. The purpose of these experiments was to determine whether patients showed disturbances of gamma synchrony compared to controls, and to establish the relationship of any such disturbances to medication levels, symptom profiles, duration of illness, and a range of psychophysiological variables.

**Results:** In the 100 normals, responses to target stimuli were characterized by two bursts of synchronous gamma oscillations, an early ("evoked") and a late ("induced") synchronization, with different topographic distributions. Only the early gamma synchronization was seen in response to background stimuli. The main variable modulating the magnitude of these gamma synchronizations from epoch to epoch was pre-stimulus EEG theta (3-7 Hz) and delta (1-3 Hz) power. Early and late gamma synchrony were also associated with N1 and P3 ERP component amplitude across epochs. Across subjects, the early gamma synchronization was associated with shorter latency of the ERP components P2, N2 and P3, smaller amplitude of N1 and P2, and smaller pre-stimulus beta power. The control analyses showed that these gamma responses were specific to a narrow frequency range (37 to 41 Hz), and were not present in adjacent frequency bands. The responses were not generated by EMG contamination or volume conduction.

In the 35 patients with schizophrenia, significant abnormalities of both the early and late synchronizations were observed compared to the 35 normal controls, with distinctive topographic characteristics. In general, early gamma synchrony was increased in patients compared to controls, and late gamma synchrony was decreased. These gamma synchrony disturbances were not related to medication level or the four summed symptom profile scores (positive, negative, general and total). They were, however, associated with duration of illness, becoming less severe the longer the patient had suffered from the disorder. The disordered gamma synchrony in patients was not
secondary to abnormalities in other psychophysiological variables, but appeared to represent a primary disturbance.

**Discussion:** The early synchronization may relate to the binding of object representations in early sensory processing, or, given that a constant inter-stimulus interval was employed, may be anticipatory and related to active memory. The late response is probably involved in binding in relation to activation of the internal contextual model involved in late expectancy/contextual processing ("context updating" or "context closure") for target stimuli.

The across epochs effects may relate to whether the focus of attention immediately prior to stimulus presentation is internal or is directed at the task. The across subjects effects suggest that a larger magnitude of the early gamma synchronization might indicate that the subject maintains a more stable and less ambiguous internal representation of the environment, that reduces the complexity of input and facilitates target/background discrimination and subsequent processing. The early gamma synchronization findings in patients with schizophrenia suggest that anticipatory processing involving active memory and forward-prediction of the environment is subject to "over-binding" or the formation of inappropriate associations. The late synchronization disturbances may reflect a fragmentation of contextual processing, and an inability to maintain contextual models of the environment intact over time.

**Conclusion:** This research demonstrates the potential importance of integrative network activity as indexed by gamma phase synchrony in relation to normal cognition, and the possible broad relevance of such activity in psychiatric disorders. In particular, the application in this study to patients with schizophrenia showed that an impairment of brain integrative activity ("missing links") might be a key feature of this illness.
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To Julia
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