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Auditory gating deficits in schizophrenia: unimodal or heteromodal dysfunction?

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Failure filtering out redundant auditory information is the most replicated neurophysiological abnormality observed in patients with schizophrenia. However, the brain structures involved in this deficit remains obscure. Two main hypotheses have been proposed to explain this phenomenon. The first maintains that the auditory gating deficit in schizophrenia is related to abnormal function of microcircuits within the hippocampal formation. The second hypothesis proposes that the deficit may be linked to impaired prefrontal cortex function. In both scenarios, auditory gating is conceptualized as a process dependent on the functional indemnity of cortical areas that integrate information from different sensory modalities. When filtering out redundant information, heteromodal cortices (hippocampal formation or prefrontal cortex), ensure that redundant stimuli do not reach higher-order levels of information processing in the brain and do not interfere with working memory performance. Findings from our lab, using magnetoencephalography (MEG), and data from other labs using electroencephalography (EEG), suggest an alternative hypothesis. We hypothesize that auditory gating deficit in schizophrenia is due to the abnormal function of unimodal microcircuits within left auditory cortex, independent from abnormalities in heteromodal cortices. Explaining whether auditory gating deficit in schizophrenia is determined by a primary dysfunction of unimodal or multimodal cortices may help elucidate the mechanisms involved in the sensory information overload and the characteristic cognitive deficits found in this disorder.

Key words:
Auditory gating. Failures. Schizophrenia. Cognitive deficits.

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Fallos en el filtraje de información auditiva en esquizofrenia: ¿disfunción de cortezas uni o heteromodales?

Fallos en la capacidad para filtrar información auditiva redundante constituyen el hallazgo patológico mejor replicado en pacientes esquizofrénicos. A pesar de esto, las estructuras cerebrales involucradas en esta anormalidad no han sido claramente identificadas. Dos hipótesis han sido propuestas para llenar este vacío: la primera sostiene que los fallos en filtraje auditivo se deben a anormalidades en microcircuitos localizados en el hipocampo y la segunda que estos defectos serían causados por una disfunción de la corteza prefrontal. Ambas hipótesis suponen que el filtraje auditivo es un proceso dependiente de estructuras de integración sensorial multimodal, las cuales al regular el flujo de información desde áreas unimodales hacia estructuras de procesamiento más complejo impedirían que información auditiva irrelevante interfiriera con procesos mentales dependientes de la memoria de trabajo. Basados en datos obtenidos en nuestro laboratorio usando magenetoencefalografía y los resultados de estudios electroencefalográficos realizados en otros laboratorios se propone la hipótesis de que una disfunción de la corteza auditiva izquierda podría explicar los fallos en filtraje auditivo en esquizofrenia. Desde esta perspectiva, anormalidades en el funcionamiento de estructuras de procesamiento sensorial unimodal, independientemente del estado funcional de estructuras multimodales, podrían estar en la base de los defectos en filtraje auditivo en esta enfermedad. Clarificar si anormalidades en procesos dependientes o independientes de estructuras heteromodales explican los defectos en filtraje auditivo en esquizofrenia permitirá una mejor comprensión de la fisiopatología de esta enfermedad e idealmente el desarrollo de mejores tratamientos para los defectos cognitivos causados por sobrecarga de información irrelevante en estos pacientes.

Palabras clave:
Filtraje auditivo. Fallos. Esquizofrenia. Defectos cognitivos.

INTRODUCTION

The ability to maintain and organize mental representations for brief intervals during a time period when original items are no longer available to perception is known as working memory[16,20,36]. This ability depends in part on the number of objects that may be maintained on-line for the correct performance of the task at hand[7,17,82]. Most healthy persons can only maintain a maximum of 7 objects in mind for a short time period[63]. In contrast to these working memory limitations, a variety of stimuli are constantly recorded in the peripheral sensory organs. Consequently, optimum working memory performance curtails simple sensorial information from reaching brain structures that control high-order cognitive processes in the central nervous system[82].

Failure in sensory gating has been proposed as one of the main culprits of cognitive dysfunction in schizophrenic patients[1,11,19,28]. Failure inhibiting neuronal responses evoked at latencies of 50 milliseconds post-presentation of the second of two identical auditory stimuli is the best replicated neurophysiological abnormality in schizophrenic patients[13,43]. First-degree relatives of schizophrenic patients demonstrate similar abnormalities[18,69,74,83,84]. The results of these investigations suggest that the auditory gating deficit observed in schizophrenic patients is not due to chronic exposure to antipsychotics or secondary schizophrenic psychosis instead, genetic abnormalities may explain this deficit[84]. Genetic polymorphism affecting the expression of the gene encoding the α-7 sub-unit of the nicotinic receptor for acetylcholine is associated to auditory gating deficits in non-schizophrenic individuals and occurs more frequently in families with high aggregation of schizophrenia[33,55]. These findings are particularly relevant because: *a)* post mortem studies in patients with schizophrenia have found a decrease in the expression of type α-7 nicotinic receptors in brain regions involved in processing auditory information, such as hippocampus[31], reticular activating system[15], prefrontal cortex[39] and cingulate cortex[60]. In addition, rats chronically treated with haloperidol do not show these decrements, making it unlikely that chronic exposure to antipsychotics will account for these abnormalities[14]; *b)* tobacco consumption or nicotine patches transiently normalize auditory gating deficits in schizophrenic patients and their first degree relatives[3,4]; *c)* drugs that directly or indirectly harness nicotinic receptors' activity, such as clozapine, ondansetron and tropisetron, also revert these deficits[5,54,55,56,75], and *d)* an increase in the prevalence and severity of nicotine addiction has been observed in patients with schizophrenia and in their first degree relatives in multiple studies[23,24,51,58,68,86,88].

Taken together, these findings seem consistent with the hypothesis that the auditory gating deficit in schizophrenia could be determined by genetically transmitted abnormalities affecting the expression of nicotinic receptors in brain areas that are critical for normal auditory gating[59]. Thus, the increased tobacco consumption reported in individuals from families with high aggregation of schizophrenia could be explained as an attempt to reduce the cognitive deficits associated with the interference of irrelevant auditory information in working memory tasks[7,17,72,82].

In spite of the heuristic value of this model, two unresolved issues question the relevance of auditory gating deficit in schizophrenic patients as a strategy to understand the pathophysiology of this disease. First, the anatomical structures involved in this abnormality remain obscure. Second, it has not been possible to establish any clear correlation between extent of the auditory gating deficit, degree of impaired performance on neurocognition and severity of symptoms in schizophrenic patients[70]. Thus, in the absence of clearly identified anatomical substrates and functional consequences, although a well replicated finding, the schizophrenia auditory gating deficit may be irrelevant. In this review, we will discuss the results of a series of studies conducted in our laboratory that provide significant information to explicate the neural substrates or normal and disordered gating and its clinical relevance.

In the first part, the hypothesis that hippocampus or prefrontal cortex is responsible for the auditory gating deficits in schizophrenia is critically evaluated. In the second part, we present data indicating that the generators of the auditory gating deficits at latencies of 50 milliseconds in schizophrenic patients are located in the superior temporal gyrus, within the left auditory cortex. In the third part, we present data indicating that the better temporal and spatial resolution of magnetoelectroencephalographic (MEG) techniques make it possible to better explicate the relationships between auditory gating deficits and failures in working memory observed in schizophrenic patients. Finally, in the last section of this review, we pose questions to be answered and propose future research.

Dysfunction of heteromodal cortices and gating deficit: role of the hippocampus?

The hypothesis that dysfunctional hippocampal microcircuits may be responsible for auditory gating deficits in schizophrenic patients is based on electrophysiological studies conducted in rats[2,32]. In these animals, extracellular recording made it possible to show that neuronal responses evoked at 40 post-milliseconds post-auditory stimulation can be detected in the hippocampal formation. Interestingly, it is at similar latencies of 50 milliseconds that the suppression of neuronal responses evoked by the second of two identical auditory stimuli has been demonstrated by electroencephalographic (EEG) recordings in the cranial vertex of healthy volunteers and schizophrenic patients[1]. Moreover, a decrease in the amplitude of the electrical activity evoked by the second of two identical auditory stimuli, using the paired click paradigm, has also been demonstrated by electrodes implanted in the hippocampal formation

of laboratory rats[2]. Based upon these observations, it has been proposed that localized microcircuits in the hippocampal formation could be the generators of electrical activity recorded at 50 milliseconds in the scalp of healthy subjects and schizophrenic patients, using the paired click paradigm[32]. In support of this hypothesis, pharmacological manipulations that enhance cholinergic neurotransmission mediated by nicotinic receptors improve the capacity to reduce the neuronal responses evoked by the second stimulus in the hippocampal formation of these animals. These results concur with what happens in schizophrenic patients receiving drugs that stimulate nicotinic receptors[75]. Likewise, lesions of the cholinergic pathways innervating the hippocampal formation are associated with auditory gating deficits in laboratory rats similar to those observed in schizophrenic patients[6]. Furthermore, electrophysiological studies have revealed that a subtype of gabaergic interneurons in hippocampal formation of the rat express α-7 type nicotinic receptors. Thus, drugs enhancing α provide further α-7 nicotinic receptor activity could increase the activity of these interneurons, which in turn may lead to a better capacity to inhibit neuronal responses evoked by redundant auditory information[29,44]. The reported abnormalities found in the hippocampal structure and function of schizophrenic patients[21,47,81,89] and in their first degree relatives[73,80] provide further evidence to this hypothesis.

Two studies that failed to establish a relationship between the extent of auditory gating deficits in schizophrenic patients and impaired performance on hippocampal dependent[19,45], argue against the hippocampal hypothesis of auditory gating deficit in schizophrenia. In addition, no correlation has been reported between the magnitude of structural abnormalities in hippocampal formation and the magnitude of auditory gating deficits in these patients. Finally, preliminary studies conducted in our laboratory have not found any correlation between auditory gating deficit and failure in the capacity to learn a version of the Virtual Morris Water Maze test or perform on the Weschler's logical memory test, two tasks dependent on hippocampal function.

To understand these inconsistent findings between animal models and human studies, it seems necessary to keep in mind that neuronal activity evoked during the paired click paradigm at 40 millisecond latencies can be recorded in the hippocampal formation of the rat does not necessarily mean that the same latency corresponds with equivalent brain regions in the human brain, since human auditory tracts are much longer. Given that the evolution of the central nervous system in mammals has entailed an increase in the number of synapses separating primary sensory from heteromodal cortices[62], and that the distance between these areas is considerably greater in the human brain, it seems unlikely that evoked responses at 40 millisecond latencies in the rat brain correspond with the same brain regions activated at these latencies in the human brain. Consistent with this tenet, two studies of epileptic patients prior to surgery for refractory epilepsy that recorded electrical activity directly at the hippocampal formation found that neural responses were evoked at latencies of 250 to 300 millisecond latencies[10,38]. Thus, these intracerebral recording findings in epileptic patients support the hypothesis that, given the existence of longer nervous tracts and a greater distance to cover between the auditory cortices and hippocampus in the human brain, much more time would be necessary for recruiting hippocampus during auditory processing in humans than in rats. Likewise, preliminary investigations conducted in our laboratory using new strategies of data analysis generated by magnetoencephalography have not found evidence of activation of hippocampal formations at 50 to 100 millisecond latencies in schizophrenic patients or healthy controls during the paired click paradigm. Moreover, we found that the parahippocampal cortex is recruited at latencies of 75 ms. These findings seem to be especially interesting if we consider that activation of the endorhinal cortex, a brain region communicating the parahippocampus with the hippocampus, has been recently found at 150 ms latencies during the paired click paradigm[10].

Taken together, the data gathered so far seem inconsistent with the hypothesis that abnormalities in the hippocampal formation of patients with schizophrenia play a relevant role in auditory gating deficit observed at 50 or 100 millisecond latencies. Since mounting evidence suggests that parahippocampal structures could play a key role in the detection of novel versus familiar sensorial stimuli[37,76], it is possible that while detection of novelty events in rats occur at the level of the hippocampal formation, it occurs at the parahippocampus level in human and nonhuman primates. Thus, it is possible that abnormalities in the structure and function of the parahippocampus play a relevant role in the auditory gating processes occurring later, at latencies of 100 milliseconds or more in humans.

Thus, if the hippocampus plays a role in auditory gating, this role is probably restricted to events occurring at latencies of 200 or more milliseconds after the 1st or 2nd click in the paired click paradigm. Using MEG in normal controls and patients with schizophrenia, our group has reported hippocampal activation at latencies of 250 to 400 ms while subjects were engaged in hippocampal dependents tasks[41]. These findings indicate that hippocampal activation can be detected using MEG. Thus, the absence of activation observed at latencies of 50 to 100 milliseconds during the paired click paradigm is not likely due to a lack of sensitivity of MEG techniques as has been argued in the past[32]. The next step to further support this hypothesis is to demonstrate that hippocampal activity can be reliably detected at 250 to 300 ms latencies during the paired click paradigm.

Dysfunction of heteromodal cortices and gating deficit: role of prefrontal cortex

The hypothesis that auditory gating deficit in schizophrenia could be related to prefrontal cortex dysfunction is

based on two sources. The first, based on studies of the neuropyschological basis of the selective attention needed to exclusively focus on the necessary clues to obtain the final goal, has provided increasing support for the role of prefrontal cortex in modulating the capacity to filter stimuli[22,65]. The second stems from studies of auditory gating evoked auditory responses in patients with frontal lobe lesions and suggests that patients with lesions involving the dorsolateral prefrontal cortex have auditory gating deficits during the performance of a variant of the paired click paradigm[53].

As with the hippocampal hypothesis, the hypothesis that dysfunctional prefrontal cortex structures underlie auditory gating deficits in schizophrenia finds circumstantial support in the existence of well-known structural and functional abnormalities in the prefrontal cortex in schizophrenia patients[47] and their first degree relatives[61]. In contrast, stronger support is provided by evidence of auditory gating deficit in patients with lesions of the dorsolateral prefrontal[53]. A more careful evaluation of the experimental paradigm used in these studies reveals, however, an important difference in the conditions under which these experiments were performed compared with the conditions under which the paired click paradigm is usually conducted in other studies with schizophrenic patients. In the investigation of patients with frontal lesions, subjects were asked to observe a silent movie during the paired click paradigm[53]. This is in sharp contrast with the usual way in which this test is conducted in other studies, since experimental subjects are asked to remain comfortably seated without performing any cognitive task during all the time that they exclusively attend to the stimuli from the paired click paradigm[1]. These experimental differences make problematic the interpretation of these results. Thus, although Knight et al. 1999 study leaves no doubts about the role that the dorsolateral cortex may play in auditory gating processes under conditions in which selective attention is recruited, it is not clear that the prefrontal cortex necessarily plays the same role under conditions in which experimental subjects are not performing an activity requiring the engagement of selective attention. One way to clarify this confusion would have been to measure if auditory gating deficits in patients with dorsolateral prefrontal lesions persist with the conventional version of the paired click paradigm. Unfortunately, in the Knight et al. 1999 study, only the version associated to the silent movie was used.

Auditory gating studies conducted while experimental subjects are sleeping suggest that prefrontal cortex probably does not play any relevant role in the neurophysiological processes involved in the auditory gating under conditions that do not require the engagement of selective attention[52]. These studies have shown that neuronal responses evoked by redundant auditory stimuli are effectively reduced even in stages of sleep during which prefrontal cortex is deactivated[46]. These results seem consistent with the study of the psychophysiology of auditory gating in schizophrenia that has described these abnormalities as «pre-attentive» or neural events occurring at sensory processing stages in which the effect of attention is minimum or absent[8,9,12]. Accordingly, most studies that have evaluated the effect of directing the attention of experimental subjects to auditory stimuli generated during the paired click paradigm have found minimal or no effect on the auditory gating at 50 millisecond latencies[40,49,87]. Conversely, these same manipulations revealed increasing amplitude of the potentials evoked at 100 millisecond latencies when the attention of experimental subjects is directed to auditory stimuli[40,87]. Likewise, auditory gating studies conducted while subjects were asleep found that, in opposition to what happened with auditory gating at 50 ms, gating at 100 millisecond latencies was profoundly affected during sleep[52].

Taken together, the results of these studies seem consistent with the hypothesis that potentials evoked at 50 millisecond latencies are generated by brain structures that have a reduced capacity to exert modulatory influences or perform selective attention tasks. Neuroanatomic studies have demonstrated that, conversely to secondary auditory cortices, primary auditory cortices do not connect directly with the prefrontal cortex. Thus, it is possible that manipulations of attention that affect the amplitude of neural responses evoked at 100 milliseconds modulate the excitability of cortical areas of secondary auditory processing. On the other hand, auditory gating at 50 milliseconds latencies may occur in primary auditory cortices, with no direct connection to prefrontal cortex. In agreement with this model, the corticography study conducted in epileptic patients prior to surgery found activation of prefrontal cortex structures only at latencies of 86 milliseconds[38]. Thus, auditory gating at latencies of 50 milliseconds may be a physiological process occurring independently of prefrontal cortex activation.

In summary, the analysis of the available evidence does not seem consistent with prefrontal cortex being a player in auditory gating deficits occurring at latencies of 50 milliseconds under conditions in which selective attention is not recruited. Conversely, auditory gating deficits at latencies of 100 or more milliseconds could be determined by abnormalities in the function of the prefrontal cortex or other brain structures involved in selective attention tasks such as the parietal cortex or anterior cingulate.

Thus, although available evidence does not support the hypothesis that abnormalities in prefrontal cortex function or hippocampal formation underlie auditory gating deficits at latencies of 50 ms in schizophrenic patients, other heteromodal processing structures such as parietal cortex or cingulate cortex may still be involved in these deficits.

Dysfunction of heteromodal cortices and auditory gating: testing the hypothesis

Investigations aimed at evaluating whether auditory gating deficits in schizophrenia involve other sensory modali-

ties were developed in our laboratory as an strategy for evaluating the validity of the heteromodal dysfunction hypothesis as cause of these abnormalities. The rational behind this strategy was that if auditory gating deficits are caused by abnormalities in the structure or function of heteromodal brain areas, then it would be expected that these deficits may include other sensory modalities[26]. A paradigm to assess the capacity of filtering redundant somatosensorial information was developed. The median nerve was stimulated electrically in a manner intensive enough to be perceived consciously by the subjects in a non-painful way. Then, paired stimuli separated by 75 milliseconds were presented every 5 seconds in a similar way to the paired click paradigm. These studies were conducted using combined MEG and MRI techniques similar to those used in our auditory gating studies. Electromagnetic activity evoked at latencies of 20 milliseconds post-stimulation was localized in the primary somatosensory cortex without finding deficits in the capacity to reduce the amplitude of neural responses evoked by redundant somatosensory stimuli in schizophrenic patients. However, bilateral deficits were found at 100 milliseconds latencies in cortical areas corresponding consistent with the secondary somatosensory cortex[26].

Overall, these studies suggest that sensory gating at latencies of 20 milliseconds in the somatosensorial pathway and 50 milliseconds in the auditory pathway are probably not dependent on dysfunctional multimodal structures because if this were the case, it would have been expected that deficits in both modalities would be present in schizophrenia patients. Gating deficits at 100 milliseconds in the somatosensory modality raise the possibility that later deficits in sensory processing in schizophrenic patients are caused by multimodal structure dysfunction. If this hypothesis were correct, it would be expected that sensory gating deficits at short latencies are specific of the auditory modality and that gating deficits at latencies of 100 milliseconds are common to several sensorial modalities. Consistent with this hypothesis, auditory information gating deficits at 50 milliseconds seem specific of the left auditory cortex, while bilateral deficits at 100 milliseconds were detectable by our group in both auditory cortices in cortical regions consistent with the location of the secondary auditory cortices[42].

In summary, the results of these investigations seem consistent with the hypothesis that deficits in early sensory gating in schizophrenic patients affect unimodal brain structures only in the left auditory pathway, while deficits in information gating at later latencies affect bilaterally both the auditory and somatosensory modalities. These later deficits could be caused by dysfunction of a heteromodal integration structure such as prefrontal cortex, hippocampal formation or parietal cortex, just to mention some possible candidates. This model would predict that in schizophrenic patients bilateral abnormalities in visual, gustatory or olfactory information gating could be demonstrated at latencies of 100 or more milliseconds but not at shorter latencies.

Dysfunction of unimodal cortices and auditory gating: primary auditory cortex

Difficulties determining the brain structures involved in auditory gating observed in schizophrenic patients originate in the limited spatial resolution that characterizes EEG techniques[25]. Thus, the electrical activity recorded at latencies of 50 milliseconds in the cranial vertex can, in principle, be generated by practically any brain structure involved in the auditory information processing. During the last five years our laboratory has been studying sensory gating with high density EEG, MEG and sMRI. carrying out investigations combining the high temporal resolution characteristic of combined MEG and MRI. Through this approach have established that the neural generators of M50 (the magnetic counterpart of P50) localizes to the superior temporal gyrus bilaterally, consistent with the auditory cortex. The MEG signal accounts for 97% of the variance in the electrical activity recorded by the electrode located in the cranial vertex in control subjects, in contrast to 86% of the variance in subjects wit schizophrenia[48]. These studies suggest that in normal control subjects at latencies of 50 milliseconds, microcircuits located in the auditory cortex may be processing and filtering redundant auditory information without involving heteromodal structures such as hippocampal or prefrontal cortex formation. In patients with schizophrenia, on the other hand, although most of the electrical activity recorded in the vertex is originated in the auditory cortices, one or several additional brain regions may be undergoing activation[48]. Confirming the validity of these findings, recent preliminary studies applying a new data analysis technique for MEG (Huang et al., 2006) that permits better localization of electromagnetic activity generators located in the prefrontal cortex and temporal lobe have shown neural activity evoked at latencies of 50 milliseconds is mostly restricted to the auditory cortex in control subjects. Conversely, in schizophrenia patients additional foci of activation have been observed in the left and right lateral prefrontal cortex. If these preliminary findings are confirmed, these studies will provide even stronger support to the hypothesis than under normal conditions, redundant auditory information gating at latencies of 50 ms is performed in unimodal auditory structures independent of activation of heteromodal structures. From this perspective, the hypothesis that the deficit in auditory gating at latencies of 50 milliseconds in schizophrenia is determined by abnormalities in auditory cortices becomes more certain. Consistent with this hypothesis, auditory gating deficits were demonstrated only in the left auditory cortex[77] and the intensity of these deficits was found to be directly correlated with the magnitude of cortical thickness decrements observed in this brain region in patients with schizophrenia[78]. These findings seem consistent with the fact that selective abnormalities in the structure of the left auditory cortex have been reported in schizophrenic patients in several independent studies[34,47,50].

A different picture was found at latencies of 100 ms. At these latencies, auditory gating deficits were found bilater-

ally in both auditory cortices. This finding seems consistent with the hypothesis that auditory filtering processes at longer latencies in cortical areas probably corresponding with secondary auditory cortices could be determined by functional abnormalities in heteromodal structures which control the flow of information top-down. Consistent with this idea, bilateral deficits in somatosensory information gating were also observed at latencies of 100 milliseconds in cortical regions consistent with the secondary somatosensory cortex[25]. Likewise, no abnormalities were found in the somatosensory gating at shorter latencies, consistent with the fact that structural abnormalities affecting primary sensory cortices are specific to the left auditory cortex in schizophrenic patients[77,78].

Cognitive dysfunction and auditory gating deficits in schizophrenia

The hypothesis that the sensory gating deficit may underlie cognitive dysfunction in schizophrenia has been suggested by several investigators[1,11]. We would expect that patients with more pronounced deficits gating redundant auditory information would show more prominent cognitive abnormalities. At least five studies have aimed at establishing a relationship between auditory gating deficit and cognitive impairments in schizophrenic patients. One study found a weak correlation between auditory gating deficit and the scores on the attention subscale of the Sale for the Assessment of Negative Symptoms (SANS)[28]. These findings were not confirmed in our patient population[78]. Similar negative results were recently reported by another group[57]. In another study, a weak correlation was found between auditory gating deficit and increases in response latency in the digit cancellation test, a test of sustained attention[19], however there is no replication of this study result thus far. Two studies assessing the relationship between auditory gating deficit and abnormalities in hippocampal dependent tests found no correlation[19,45].

Overall, the results of these studies question the predictive validity of auditory gating deficit in schizophrenia's cognitive dysfunction. An alternative interpretation would be that the lack of correlation between auditory gating deficit and cognitive impairment may be accounted for by lack of accuracy of the techniques used to measure auditory gating[25]. Until recently, this phenomenon has been measured mostly using an EEG electrode preferably implanted in the cranial vertex. The electrical activity thus recorded corresponds to the sum of events potentially occurring in any brain region recruited, normally or pathologically, during the performance of this test.

On the other hand, findings from our studies with combined MEG and sMRI demonstrate that the auditory gating deficit in schizophrenia is localized in the left but not right auditory cortex schizophrenia[77]. Furthermore, studies combining MEG/MRI with conventional EEG show that additional brain structures are recruited during this test only in schizophrenic patients[48]. Moreover, preliminary data using new data analysis techniques developed in our laboratory suggest that dorsolateral prefrontal cortex may be one of the additional structures recruited in schizophrenic patients during the paired click paradigm. Thus, the electrical activity recorded at latencies of 50 milliseconds at the vertex of the schizophrenic patients could represent the sum of activities generated in the left and right auditory cortices plus the pathological activity generated in the dorsolateral prefrontal cortex. It is possible that the effect of abnormal activity at left auditory cortex on cognition is not detected by techniques in which this dysfunctional activity is analyzed along with activity generated in other brain regions. Consistent with this hypothesis, inter and intra-individual reliability studies of auditory gating using conventional EEG show that the test-retest reliability of these measurements is low, when compared to gating measurements obtained via MEG. Likewise, measures of auditory gating using MEG/MRI showed a significant correlation between auditory gating deficits in the left auditory cortex and deficits in working memory tasks in schizophrenic patients[77]. More recently, these results have been replicated with a larger patient sample and extended the findings to include other cognitive tests. We found strong correlation between the magnitude of auditory gating deficit of left auditory cortex and impairments in the Wisconsin card test and the Rey Auditory word list learning test, two neurocognitive tasks dependent on left prefrontal activity. On the other hand, no correlations were evident when cognitive performances on working memory tasks were correlated with auditory gating measures using EEG recordings obtained at the vertex[77]. Similarly, no correlations between auditory gating deficit measured at the vertex (Cz) and performance on the Wisconsin test have been reported by two other groups[28,57].

Taken together, the results of these studies suggest that schizophrenia's left auditory gating deficit is localized to the left auditory cortex and could be a good predictor of working memory impairment in schizophrenic patients. EEG techniques used so far may lack the appropriate spatial resolution to clearly detect these relationships.

From the pathophysiological point of view, these findings provide the empirical basis to hypothesize that sensory gating deficit in schizophrenia patients may play a major role on their impaired performance on working memory tasks. Thus, left auditory gating deficit predicts working memory impairments only in patients and not in the controls[77]. This interpretation seems to make sense if irrelevant auditory information have a negative impact on cognition only under conditions in which the brain structures in charge of supporting and organizing mental representations are already dysfunctional and thus more vulnerable to the harmful effects of an overload of sensory information. From this point of view, a healthier prefrontal cortex would have a larger functional reserve to tolerate the overload of information caused by the auditory gating deficit. From this

perspective, the fact that up to now we have observed activity of the prefrontal cortex only in schizophrenic patients and not in the controls during the performance of the paired click paradigm seems particularly relevant. These findings are consistent with the hypothesis that abnormal activation of the prefrontal cortex caused by overload of redundant auditory information could affect the capacity of this structure to store and reorganize information during working memory tasks or during tasks in which learning word lists, as in the Rey Auditory Verbal Learning test, is required.

On the other hand, it has not been possible to detect any correlation between auditory information gating deficit and performance on hippocampal dependent cognitive tasks, such as Weschler's logical memory test or Virtual Morris Water Maze task. These negative findings seem consistent with the idea that only tasks directly dependent on short term memory systems activity are vulnerable to the harmful effect of information overload provoked by auditory gating deficit in schizophrenia. From this point of view, it is possible that brain systems (such as the hippocampus), that normally process and store large amounts of information, are less vulnerable to the harmful effect of sensory information overload from unimodal auditory cortices.

An alternative interpretation would be that the correlation between the magnitude of the deficit observed in auditory gating and the deficits in working memory dependent tasks in schizophrenic patients would be the result of prefrontal cortex dysfunction. From this point of view, the auditory gating deficit observed in the left auditory cortex would be the consequence and not the cause of the abnormalities in prefrontal cortex dependent cognitive tasks. In comparison with this interpretation, however, neuroanatomical and electrophysiological data reviewed in the previous section do not seem to support a dominant role of the prefrontal cortex on the activity of primary auditory cortex at latencies of 50 milliseconds. Consistent with this hypothesis, genetic studies performed in our laboratory using polymorphism of the gene that encodes catecol-o-methyltransferase (COMT), a key enzyme in the regulation of the prefrontal function and structure[27,35,67,71], as a marker of prefrontal function has not demonstrated up to now any correlation with the auditory gating deficit at latencies of 50 milliseconds in the left auditory cortex. However, a significant correlation has been found with the gating magnitude at latencies of 100 milliseconds in this same cortical region. These genetic-functional correlations seem to add solid support to the idea that gating at latencies of 50 milliseconds is, in fact, a process which is independent of prefrontal function under conditions in which selective attention is not engaged.

A third interpretation for the correlation between left auditory gating deficit and working memory impairment would be that these two variables are associated and depend on a third factor. From this point of view, no direct causal association would exist between auditory gating deficit and working memory deficits in schizophrenia since both phenomena would be determined by a third factor not included in the analysis up to now. For example, a global deficit in the development of left brain hemisphere in schizophrenia that leads to a defective neurodevelopment of the prefrontal cortex and the left auditory cortex. In this way, auditory gating deficits and prefrontal cortex dependent cognitive impairment would appear falsely correlated without any causal relationship between both phenomena. Although this explanation is certainly possible, it would also have to explain why a deficit in the development of the left hemisphere does not affect the hippocampus so that a relationship between left auditory gating deficit and impaired left hippocampal dependent tasks could be established.

Based on the data available, we believe that the simplest interpretation is that auditory gating deficit, determined by abnormalities in the function and structure of microcircuits located in the left auditory cortex, lead to redundant information overload in left prefrontal cortex of schizophrenic patients significantly interfering in the performance of tasks dependent on the capacity to support and organize mental representations during the short time intervals during which the objects represented are inaccessible to perception. A new generation of studies combining MEG/MRI during the performance of working memory dependent tasks in the presence or absence of redundant auditory information may experimentally evaluate this hypothesis more directly.

Cognitive dysfunction and gating deficit in schizophrenia: new questions

In the previous sections, we have tried to show how growing empirical evidence supports the hypothesis that redundant auditory information gating deficit in left primary auditory cortex could contribute to the abnormalities in working memory seen in schizophrenic patients. At the same time, we have tried to establish the hypothesis that later deficits, at latencies of 100 milliseconds, could depend on abnormalities in higher processing structures in the prefrontal, parahippocampal and/or parietal cortex. To evaluate this hypothesis more directly, studies are needed that directly show the mechanism through which auditory gating deficit at latencies of 50 milliseconds could disturb prefrontal function. Preliminary observations using new techniques of data analysis of MEG elaborated by one of our collaborators, Dr. Minxiong Huang, show that the lateral prefrontal cortex is pathologically activated during the performance of paired click paradigm in schizophrenic patients but not in the controls. Thus, pathological activation of prefrontal cortex while listening to the paired clicks could possibly impair the capacity of this structure to take charge of more relevant information. Recent studies show that subjects with better performance in working memory tests are those who activate fewer brain regions during the performance of

these tasks[2]. These findings have been interpreted as evidence in favor of the hypothesis that the capacity to contain activation to specific brain areas during the representation of relevant sensory information is a key condition for optimal intellectual functioning[7,17]. In sum, our preliminary findings suggest means of testing interesting hypotheses to further elucidate the neural basis of sensory gating deficit in schizophrenia.

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