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Sensory Gating: A Translational Effort From Basic to Clinical Science

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Abstract

Sensory gating (SG) is a prevalent physiological process important for information filtering in complex systems. SG is evaluated by presenting repetitious stimuli and measuring the degree of neural inhibition that occurs. SG has been found to be impaired in several psychiatric disorders. Recent animal and human research has made great progress in the study of SG, and in this review we provide an overview of recent research on SG using different methods. Animal research has uncovered findings that suggest 1) SG is displayed by single neurons and can be similar to SG observed from scalp recordings in humans, 2) SG is found in numerous brain structures located in sensory, motor and limbic subregions, 3) SG can be significantly influenced by state changes of the organism, and 4) SG has a diverse pharmacological profile accented by a strong influence from nicotine receptor activation. Human research has addressed similar issues using deep electrode recordings of brain structures. These experiments have revealed that 1) SG can be found in cortical regions surrounding hippocampus, 2) the order of neural processing places hippocampal involvement during a later stage of sensory processing than originally thought, and 3) multiple subtypes of gating exist that could be dependent on different brain circuits and more or less influenced by alterations in organismal state. Animal and human research both have limitations. We emphasize the need for integrative approaches to understand the process and combine information between basic and clinical fields so that a more complete picture of SG will emerge.

Keywords

Auditory Evoked Response; Hippocampus; Inhibition; Nicotine; Prefrontal Cortex; Stress; Striatum

INHIBITORY GATING: CLINICAL RELEVANCE

The ability of the CNS to inhibit or suppress the response to incoming irrelevant sensory input is a fundamental protective mechanism that prevents the flooding of higher cortical

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centers with irrelevant information.[1] This inhibitory capacity of the CNS has been termed "sensory gating" (SG). To evaluate SG two identical stimuli (S1 and S2) are delivered with a short time interval of 500 ms between the clicks and a longer time interval of at least 8 seconds between the pairs.[2] It is postulated that the first stimulus (S1) generates a memory trace that reverberates in a neural circuit (presumably in the hippocampal region). When the second stimulus arrives it is compared to the memory trace and is then actively inhibited as it contains no new information.

SG is operationally defined as the ratio of the amplitude of the response to S2 stimuli to the amplitude of responses to S1 stimuli multiplied by 100. Lower numbers reflect stronger attenuation of irrelevant input and thus better gating capability. Abnormalities in sensory inhibition were demonstrated in a number of psychiatric conditions.[3] P50 auditory gating deficit is one of the best established biological traits associated with schizophrenia.[4,5] Despite the repeated demonstration of abnormal gating in psychiatric disorders, the basic mechanisms involved in filtering repetitious incoming irrelevant stimuli (particularly on a physiological level) are not well-defined.

In this review, we discuss recent work on SG from basic research studies to human clinical science and note similarities and differences between the approaches. Overall human and animal research have significant value, and by testing SG using identical paradigms with different models and populations, the data achieved from combined efforts will yield the greatest information.

INHIBITORY GATING: ANIMAL RESEARCH

SG has been examined using chronic microwire implants located directly in specific brain structures or even simultaneously in multiple brain regions.[6–11] Moxon and colleagues[11] performed single unit recording from several regions including brainstem, thalamus and primary auditory cortex. They found the most robust SG of auditory input outside of the primary auditory pathway. Similar non-auditory IG has been the focus of a number of papers on IG within the hippocampus.[12,13] These structures are not crucial for auditory processing yet rapidly and consistently monitor auditory input for functions related to intrinsic neural computations. Recent work has focused on SG in a set of limbic and motoric brain regions and has utilized chronic neurophysiological recording for an extended time period of multiple days. Long-term simultaneous single unit and local field potential (LFP) recording has allowed us to examine the stability of gating over several days and across different motivational states.

We have recorded these signals from the amygdala,[7] striatum,[8] medial prefrontal cortex (mPFC)[10] and midbrain dopamine cell region.[6] In each structure, the neural responses to the tones could be categorized into excitatory short and long-term activations and a set of inhibitory responses. The amplitudes of the responses decreased over daily sessions but gating remained relatively intact. The percentage of single units that showed gating varied between brain regions, with the amygdala and mPFC having a high proportion of units that gated auditory input with no single units displaying equal responses to both stimuli. In contrast, the basal ganglia regions had units that displayed no gating. In the midbrain region,

putative dopamine neurons did not show gating while putative GABAergic neurons did display persistent gating. Since we obtained both single unit and LFP data from the same recording wires, we analyzed the relationship between amplitudes of the responses and degrees of gating for each wire for both signals. There were no significant relationships between single unit and LFP responses in striatum and few relationships were found in mPFC.[8,10] These findings support the idea that input and output signals can vary dramatically in terms of the strength of local inhibitory control. SG would vary depending upon local inhibitory circuits and local afferents.

We were interested in the influence of motivational state changes on local SG in these diverse brain regions. Others have shown that gating or auditory responsiveness can be altered by acute or transient state changes.[14–18] An acute stressor of saline injection led to an increase in the amplitude of the existing neural responses to tones.[7,8] SG was actually strengthened meaning that the increase in the amplitude was primarily during the initial tone response and less during the subsequent “test” tone presentation. This type of modulation has implications of the role of amygdala in emotional processing and appears similar to the types of the changes seen in auditory responding after fear conditioning.[19] Other motivational state manipulation such as hunger led to a weakening of SG found in single unit records but an enhancement of gating from LFPs.[8] This is another example of how intrinsic processes can alter the degree of inhibitory control. Finally, in the basal ganglia region of the striatum movement led to enhanced gating in the local single units suggesting that during exploration animals are better at discriminating repetitious information leading to better accuracy for novel stimuli. These results of single unit gating from structures outside of the primary auditory pathway illustrate the pervasiveness of the mechanism of rapid sensory filtering and provide insight into the potential special, unique functions for gating within individual brain regions and specific neural circuits.

Recent work has focused on the role of nicotine in SG due to the fact that a high percentage of schizophrenics smoke (80% up to 30 cigarettes/day) and smoking helps reduce negative symptoms, improve cognition and improve SG.[20–22] Animal models have been very important in elucidating the influence of nicotine on SG. Nicotine administration improves gating by single units in amygdala in freely moving rats.[9] Nicotine restores SG that has been impaired by previous amphetamine administration and this improvement is blocked by central delivery of d-tubocurarine.[23]

Stimulation of a nicotinic receptor releases nitric oxide, which in turn mediates sensory inhibition. The nicotine-induced release of nitric oxide may explain why some of the behavioral effects of nicotine have a longer time course than predicted from desensitization of nicotinic receptors. Adams and Stevens,[24] examined the disruptive effects of nitric oxide synthase on IG of auditory responses in rat hippocampus. *N -nitro-L-arginine methyl ester (L-NAME)* was continuously perfused through the ventricular system of anesthetized rats as they were tested for auditory gating. *L-NAME*, but not *D-NAME*, produced a loss of sensory inhibition, suggesting that loss of enzyme activity would alter normal sensory inhibition. Secondly, to determine if the effect of nitric oxide was presynaptic or postsynaptic to nicotinic receptors, rats with lesions of the fimbria/fornix were tested with nicotine in the presence of *L- or D-NAME*. Fimbria/fornix lesions normally reduced sensory inhibition,

which was restored with systemic nicotine injections. Lesioned rats treated with *D-NAME* showed normal sensory inhibition upon injection of nicotine; lesioned rats treated with *L-NAME* did not. This finding suggests that the release is directly from the hippocampus (postsynaptic effect) and not a presynaptic release from an afferent source (e.g., medial septum).

Metzger et al.[25] utilized two animal models: C57BL/6J mice (n 14; 8 weeks of age) and DBA/2Hsd mice (n 16; 8 weeks of age). C57BL/6J and DBA/2Hsd mice received 2 weeks of 4.2 mg/kg chronic nicotine or saline. Auditory evoked potentials were recorded before and after acute nicotine injection of 1.05 mg/kg on day 14, with a paired-click paradigm (S1/S2). Acute nicotine increased the amplitude and gating of the P20 and decreased the amplitude and gating of the N40 across all groups, primarily by acting on S1. Chronic nicotine attenuated the effects of acute nicotine on the N40. Therefore, the mouse P20 shares pharmacological response properties with the human P50. In addition, findings suggest that nicotine might increase the initial sensory response (S1), with a resulting improvement in gating of some components. Overall the animal research allows for precision in examining the local neuroanatomy and pharmacology of SG.

INHIBITORY GATING: HUMAN CLINICAL RESEARCH

In humans, direct evidence for an involvement of the hippocampus in sensory gating is difficult to obtain due to the closed electrical field nature of the electrical signal generated by the hippocampus, not allowing the recording of hippocampal activity from the scalp.[26] However, the occasional need to implant intracranial electrodes during the presurgical evaluation of patients with medically intractable focal epilepsies makes it possible to record EPs directly from the human hippocampal formation and cerebral cortex. This approach has its limitations as implantation of electrodes is always dictated by the clinical needs and not driven by theoretical considerations. Moreover, theoretically important regions (e.g., thalamic region for this study) will not be targeted due to medical as well as ethical reasons. The electrode coverage of different neocortical areas is always limited as the potential risks for the patients increase with an increasing number of implanted electrodes. Finally, there is always the risk that epilepsy might directly or indirectly affect cortical processing and the functional anatomical organization. Despite these limitations the study of cortical functions by means of invasive recordings has proven immensely useful in exploring the anatomical correlates of many cognitive functions.[27,28] Our group recorded neocortical and hippocampal responses to paired clicks with the aim of determining the extent to which different regions of the human brain contribute to sensory-gating. Our initial exploration revealed that the P50 is recordable in two distinct regions, the primary auditory cortex and the prefrontal cortex.[29] In this study, no P50 equivalent was detected in hippocampal recordings, but a later, much broader response with negative polarity and a peak latency at approximately 250 ms was observed. This late hippocampal response was strongly reduced by stimulus repetition.

The latency of human hippocampal responses are clearly different from animal studies, such as in the rat hippocampus EPs associated with sensory gating peak as early as 40 ms following auditory stimulation.[30,31] Our finding in humans suggests that the hippocampus is

involved in a later stage of auditory sensory gating. A similar conclusion can be drawn from the observation that early preattentive auditory discrimination processes as reflected in the mismatch negativity are not affected by hippocampal lesions,[32] but later EPs elicited by novel stimuli were found to be reduced by such lesions.[33] More recently we provided additional data from direct hippocampal and rhinal cortical recordings supporting the involvement of the human medial temporal lobe in the processing of simple auditory information occurring in a time frame later than the neocortical auditory evoked components.[34] This study also provided the first evidence of activation in the rhinal cortex after simple auditory stimulation and suggests different roles of the rhinal cortex and hippocampus in auditory information processing. The auditory evoked response as recorded from the central region is also of a simpler nature than the mid-latency evoked cascade obtained from human subjects.[29] Recent sensory gating studies point to the sensory gating function being more complex with at least two phases in humans. Evidence points to temporal and frontal cortices as the main brain locations mediating an early phase of gating and the hippocampus and rhinal regions mediating a later phase of sensory gating.

INHIBITORY GATING: COMPARISONS BETWEEN ANIMAL AND HUMAN RESEARCH

Animal data have been very important in providing basic information about the neuroanatomy and neuropharmacology of SG. However, translating rat studies to humans raises difficulties. There are two important limitations to keep in mind. The first is that cortical structures in the rat are very different from humans. In addition, the relative size of the two brains suggests that evoked potentials in the human should occur at longer latencies than those in the rat. Therefore, direct association between rat and the human may be difficult. These general issues should lead any researcher to be cautious about how to make the translation from between animal and human brain function. The animal work provides experimental rigor but lacks the valid neural configuration that the human work intrinsically provides.

Two major differences immerge from the literature regarding the sensory gating system in the rats and in humans. First, in the rat, the hippocampus seems to be playing a central role in the earliest evidence of gating, while in humans the role of the hippocampus may be more crucial in later stages of sensory gating.[29] Secondly, while in rats a stimulus that is getting louder causes more disruption of gating as compared to stimuli that are repeating or getting fainter (most likely reflecting less threatening stimuli),[35] in humans any change in the stimulus characteristics results in disruption of gating.[36] The rat N40 auditory evoked response (AER) has been correlated with the human P50 as both exhibit amplitude attenuation with stimulus repetition in paired-click paradigms. While the P20/N40 is the main AER component recorded from the vertex of the rat, the human response is comprised of three major components; P50, N100 and P200. Recent evidence suggests that the rat P20 is the correlate of the human P50 while the N40 of the rat response is more a correlate of the human N100.[35] These points need to be studied in more detail to fully reveal the importance of SG in normal functioning and the ways in which SG becomes impaired leading to debilitating psychiatric disease.

CONCLUSIONS

SG deficit has rapidly emerged as an important physiological marker related to psychosis. SG deficit has also been identified in other disorders where the potential for psychosis is also elevated like Bipolar Disorder[37] and Post-Traumatic Disorder.[38] SG has also been found to be deficient in a number of neuropsychiatric disorders including epilepsy,[39] Alzheimer's Disease,[40] traumatic head injury,[41] and Huntington's Chorea,[42] all disorders where the potential for psychosis is elevated. As is clear from the above review, much is still not known about the basic physiological processes underlying this complex protective function. Animal work remains very important for advancing knowledge in this field, but significant differences between the rodent and the human systems place important limitations and requires the exercise of caution when extrapolating from animal to human experiments.

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