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Influence of emotional states on inhibitory gating: Animals models to clinical neurophysiology

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Abstract

Integrating research efforts using a cross-domain approach could redefine traditional constructs used in behavioral and clinical neuroscience by demonstrating that behavior and mental processes arise not from functional isolation but from integration. Our research group has been examining the interface between cognitive and emotional processes by studying inhibitory gating. Inhibitory gating can be measured via changes in behavior or neural signal processing. Sensorimotor gating of the startle response is a well-used measure. To study how emotion and cognition interact during startle modulation in the animal model, we examined ultrasonic vocalization (USV) emissions during acoustic startle and prepulse inhibition. We found high rates of USV emission during the sensorimotor gating paradigm and revealed links between prepulse inhibition (PPI) and USV emission that could reflect emotional and cognitive influences. Measuring inhibitory gating as P50 event-related potential suppression has also revealed possible connections between emotional states and cognitive processes. We have examined the single unit responses during the traditional gating paradigm and found that acute and chronic stress can alter gating of neural signals in regions such as amygdala, striatum and medial prefrontal cortex. Our findings point to the need for more cross-domain research on how shifting states of emotion can impact basic mechanisms of information processing. Results could inform clinical work with the development of tools that depend upon cross-domain communication, and enable a better understanding and evaluation of psychological impairment.

Keywords

Cognition; Emotion; Inhibition; Rat; Electrophysiology; Startle

The updated version of the diagnostics and statistical manual has been published recently [DSM-V, 2013] with the detailed criteria that can be used for mental illness diagnosis. In addition to its use in the clinical setting, the DSM has been a guide for research on mental

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illness since its inception. The symptoms for a typical disorder cross different domains of function and can include impairments in cognition, emotion, and motivation [DSM-V, 2013]. Sparking controversy, the director of the National Institutes of Mental Health (NIMH) recently spoke out against using the strict definitions of a particular disorder to guide research. In place of a specific disorder, research groups should focus on research domains (RDocs) that bridge a variety of disorders and potentially capture the underlying pathology of mental illness more accurately. RDocs incorporate cognitive and emotional processes and specifically include: Negative Valence Systems (e.g., fear, anxiety, loss), Positive Valence Systems (e.g., reward processing and habits), Cognitive Systems (e.g., attention and memory), Systems for Social Processes (e.g., attachment and self image), and Arousal/Regulatory Systems (e.g., arousal and sleep). Historically, the NIMH research agenda is represented by and large with investigations that focus either on cognitive or affective domains. Examples include studies on working memory and cognitive deficits in schizophrenia [1]. This work attempts to reveal how the neural basis for attention and memory storage is disrupted and to determine how the loss of an ability to retain short term representations of information can lead to psychosis and symptoms of hallucinations and delusions [2]. Other work takes more of an emotional domain approach and focuses on emotion expression, recognition, and regulation [3]. The use of RDocs is supposed to be agnostic about diagnosis categories and is proposed to enable the development of new categories that arise from basic behavioral neuroscience research [4].

In popular thinking, there is a common idea that one has an ‘emotional’ and a ‘thinking’ brain, and that in many cases the two are pitted against one another. When one is optimally engaged, the other is effectively shut down. A simplified prediction from this idea would state that one must reduce or abolish intrusive emotional states to boost problem-solving ability, and that cognition is impaired when one is in an intensive emotional state. Despite the oversimplified nature of this perspective, versions of these ideas have led to independent streams of research on cognition or emotion. They have also led to a clash in terms of arguments over the supremacy of one domain versus the other [5]. Cognitive science prevailed for an extended reign, but recently other domains have risen for many reasons, not the least of which revolves around the idea that domain dissociation should be seriously reevaluated [5].

The idea of bridging emotion and cognition has swept through psychology, neuroscience, and psychiatry and delivered new ideas about how our rational problem-solving process inherently depends upon emotions and homeostatic states [6, 7, 8]. Work on animal models of emotion [9] and human neurological syndromes [10] illustrate how an interaction between functional domains is adaptive and pervasive. There are a growing number of measures that can span the breath of functional domains. The functional process of inhibition has been proposed to be crucial for every form of psychological function and all types of behavioral output. This review focuses on neural and behavioral gating as forms of inhibition, and as measures that can capture the interplay between domains as gating is expressed at multiple and diverse levels.

Inhibition as a fundamental neural process

A general and fundamental process of mental functioning is inhibition. Imagine that you are typing a manuscript in your office and the phone rings. You stop typing and pick up the telephone and commence speaking. The input of the telephone ring disrupted your ongoing behavior of writing. Just imagine another scenario in which you continue with your typing and words flow out of the 'typewriter' as if no phone ever rang at all. In this case, the telephone ringing was 'gated out'. An inhibitory process enabled the writer to continue with thoughts and efferent output of the complex idea/word production involved in writing. At the extreme, the writer would not perceive the ringing phone at all.

Inhibition has been studied as a key neural process in diverse ways. Fundamental properties of neural inhibition were revealed by Sir John Eccles using *in vitro* preparations or *in vivo* recordings of neural circuits [11]. This Nobel Prize winning effort by Eccles demonstrated the power of inhibition to control the flow of neural transmission, and to deliver patterned output that reverberated across different stages of processing. The examination of neural inhibition continues, and current neurophysiology examines inhibition in relation to sensory adaptation [12], neural oscillations [13] and neuroscience of behavior [14]. Simpler networks rely on inhibition [15] and central nervous system 'gating' via inhibition is critical at every level from spinal cord [e.g., pain, 16] to cerebellum [17] to midbrain [18] to different forebrain regions [cortex: 19; striatum: 20 2002; hippocampus: 21; amygdala: 22]. A gating function is common to all inhibitory mechanisms. The diversity arises in the functions in terms of the type of information selected and inhibited, and the way that filtered information is utilized by other brain regions. The previous and recent findings support the idea that basic inhibition functions in similar core ways in different locations, yet it also supports differences in terms of connections, information processing capabilities, and network output [23]. Neural gating via intrinsic inhibitory pathways could be part of a cognitive, emotional, or sensory process depending upon where the inhibitory mechanism is located and its impact on the neural computations, both locally and globally.

Psychological gating and sensorimotor reflexes

One way that inhibitory processes are often studied is by monitoring the primitive startle reflex [24]. In humans, this work typically includes measuring the blink reflex [2] while in animal models, the whole body startle response is measured [14]. One of the major attractions for this work is that the neural circuitry for these primitive reflexes is well known [26, 27]. It is clear that lower brain regions, including brainstem areas of the nucleus reticularis and periaqueductal grey, are critical for mediating the startle response [28, 29]. Activity in the lower brain nuclei are modulated in a strong fashion by forebrain regions mainly involved in cognitive and emotional processes. Studies have found that the startle response is altered in different ways depending upon emotional state. When animals are primed with an aversive state, startle is potentiated; when cues indicate safety, the response is dampened [30]. Forebrain regions like the nucleus accumbens have been shown to play a major role in this effect when cues or tones are paired with a rewarding outcome [31]. The emotional priming model of startle has been extensively studied in humans [32]. For

example, Grillon and colleagues have shown that experience with or anticipation of aversive shocks potentiates startle [33, 34].

Predictability may be a crucial component in modulating primitive reflexes like startle. This idea has enabled groups to emphasize the top-down modulation of startle [35, 36]. Attention has been proposed as a key cognitive mechanism involved in startle alterations. Models that focus on attention are used to investigate deficits in mental illnesses such as schizophrenia or attentional deficit disorder. The majority of the work does not promote the idea that prepulse inhibition of the startle is solely a cognitive process, but much of the work does highlight the idea that disrupting PPI could lead to impaired cognitive performance [37]. The role of inhibitory gating and cognition could be thought of as modulatory but not essential nor even necessary. Recent work has shown that different forms of gating can exist with some forms being activated during cognitive states that aid learning and memory. Other forms may proceed as gating of ‘background’ or ‘noise’ and continue regardless of the cognitive state of the organism. These ideas arise after reviewing recent work on gating and cognition. Correlational work has found significant relationships between levels of prepulse inhibition (PPI) and cognitive performance [36]. This study not only found this relationship in typical individuals but also in persons with schizophrenia. The study used a novel, modified PPI paradigm in which participants were directed to attend to the auditory stimuli (ATTEND task) or ignore the auditory stimuli and attend to concurrent visual stimuli (IGNORE task). In addition, during the ATTEND condition, participants were told to respond to trials depending upon the occurrence of the prepulse. Lower or higher PPI varied depending upon the ATTEND or IGNORE conditions and on the response versus the stimulus trial segments. Interestingly, the cognitive changes were not necessarily linked to overall PPI score, but they were intimately linked to PPI dependent upon the IGNORE or ATTEND condition. The authors’ interpretation included an idea that the effect on inhibition is linked more so to attentional processes, and not primarily linked an overall common inhibitory mechanism. To further support the role of cognitive-attentional mechanisms, a later study found that the impairment in PPI in schizophrenic patients was a consequence of attentional dysfunction [38]. This work as well as others supports the idea that PPI deficits could act as indicators for the degree of cognitive impairment in mental illness and contribute to translational research that leads to better treatments and diagnosis [39, 40]. In addition, these findings suggest that there are multiple forms of PPI with each subtype dependent upon a different psychological process.

Examples of cognitive-emotion cross-domain approach

In an attempt to advance a cross-domain approach using the prepulse inhibition paradigm, we recently examined PPI in the rat model and attempted to monitor emotional state by recording ultrasounds that the animals emit during PPI sessions [41]. We are aware of only one previous study that recorded rat ultrasounds during PPI [42], and this measure aided in the interpretation of their psychopharmacological manipulation effects on PPI. This work [42] is another fine example of cross-domain research by monitoring PPI, ultrasonic vocalizations (USVs), and examining the administration effects of phencyclidine (PCP). These researchers found that the PCP treated animals had a working memory deficit expressed by defective learning of PPI-related fear conditioning. They found this memory

deficit by monitoring rats' 22 kHz USVs during the PPI paradigm. The animals typically increased USV call emission when exposed to three consecutive days of PPI testing. A similar increase was lacking in the PCP exposed group, which suggests that repeated exposure did not produce an associative link between the context of the PPI test and the aversive loud tones. Our work was oriented in a similar way and depended on the idea that rodent ultrasounds can be an accurate measure of affective state in rats [43] as well as other animals [44]. Two major types are emitted by adult rats: a lower frequency call (22–28 kHz) related to aversive states, and a higher frequency call (50–55 kHz) emitted during positive states. Previous work has already shown that loud tone stimuli lead to the emission of lower frequency calls [45]. This study found that only a subset of animals (50–70%) emitted calls after exposure to loud tones. In these positive responders, anti-anxiety compounds such as benzodiazepines and ipsapirone significantly decreased USV emission. Exposure to loud tones was presented as a model for anxiety, and USVs were a sensitive measure for changes in anxiety during exposure. Acoustic aversive stimuli were proposed as more efficient than footshocks because of the following characteristics: 1) Auditory stimuli at the necessary loudness (90–110 dB) do not produce pain responses; 2) The perception of same loudness stimuli is reliable within and across subjects; and 3) Measurements of startle can be completed to examine co-variance with USV levels. The majority of PPI work on startle uses unpredictable trial sequences with a variable interval between trials. Different trials are used in some cases, such as with or without the prepulse, with changing loudness, or with changing latencies for the prepulse stimulus [46]. Predictability per se is not often directly or systematically manipulated. Previous work has shown that predictability is a powerful influence on emotional states and a powerful influence on rodent USV emission [43]. Classic work using predictable or unpredictable footshock described the significant impact that predictability can have on emotional, behavioral, and autonomic nervous system responses [47, 48].

We used three different types of trial sets to manipulate predictability of the PPI session. The first type of trial set was the standard variable interval set with mixed trial types. The three trial types included: 1) a PPI trial with prepulse (60 dB) and loud tone (118 dB); and 2) a loud tone (PA; 118 dB) trial with loud tone pulse alone, and 3) a soft tone (PP; 60 dB) trial with only the prepulse stimulus alone. We also used two other session types with these three trials: 1) A fixed interval for the trials and random order of trial presentation, and 2) A fixed trial order and fixed time interval. These different sessions span the gamut of least predictable (variable interval with random sequence) to most predictable (fixed timing and sequence structure in blocks of trials). Not surprisingly, 22 kHz USVs were seen abundantly in the different sessions (Fig 1). Startle was reduced in the least predictable session type compared to the other sessions, but only for the soft tone trials (PP trials) and not for any trial type with a loud tone. This was interpreted as a relative effect based on shifts in tone loudness. This was a more common occurrence during the variable session in which the soft tone was often followed by a loud tone, and startle generalized to all trials when the loudness of tones was unpredictable. In the blocked sessions, the initial block experience made a significant difference. Beginning a session with loud tone trials led to high levels of USV emission throughout the session even in the soft tone trial block (see Figure 1). In each case, it took several trials of loud tones before USV emission ramped up to high levels. Most

of these findings point to a dissociation of sensorimotor gating and emotional output in the PPI paradigm, but we found that when the animals were exposed to a second session of the same trial type, both USV emission and PPI were impacted. This effect was robust in the fixed-timing session type and was seen as a decrease in USV number as well as a greater PPI. This less aversive and higher inhibitory gating combination signifies that the emotional component can be directly related to gating as measured from the primitive reflex. A similar direct relationship was lacking in the standard PPI session repeated week to week. USVs decreased but there was no significant shift in the PPI value. So, the interaction is complex in that it depends upon predictability in the short-term and the long-term, with the former being represented by blocked trials of the experience and the latter by familiarization with the general context as well as the ongoing level of predictability during the test session. Overall, the study reflects a strategy to measure different dependent variables that bridge functional domains. The results demonstrate both segregated and integrated processes via the measures. They also provide opportunities for future exploration as to how aversive emotion during sensorimotor gating could impact the measure and how impaired emotions could interact with cognitive deficits and influence sensorimotor testing.

Psychological gating of the P50 event-related potential

Event-related potentials (ERPs) provide a means to evaluate brain signals linked to the processing of discrete events. A set of ERP components exists following stimulus presentation. Auditory sensory responses include very early brainstem evoked responses and later responses that occur 100ms after tone onset, such as the N1, N2, and P3 families of responses. In between is an interesting mid-latency response called the P50, which occurs around 50ms post auditory stimulus. Gating of the P50 response has developed into an area of investigation with basic and clinical science implications [49]. Inhibitory gating is experimentally characterized by a reduced responsiveness to redundant stimuli. The P50 component is the essential target response in the evaluation of human inhibitory gating [50, 51, 52, 53, 54]. P60 is the label given to the component when recording from local field potentials in animal models. Figure 2 provides an example grand average of a local field potential recording during inhibitory gating. The recording was completed in the rodent medial prefrontal cortex [19].

In humans, the P50 component is elicited using ERP techniques in which identical pairs of tones are presented and P50 responses to the tones are elicited and then compared. The clicks within a pair are separated by an intertrial interval of 500ms, and trial pairs are typically separated by 8 to 10 seconds [19, 50, 55, 56, 57]. In general, P50 amplitudes decrease in response to repeated stimuli and increase in response to novel stimuli [50]. P50 gating has been proposed as a pre-attentional mechanism involved in sensory information processing and the modulation of responses to stimuli [50; 58]. Healthy inhibitory gating function is thought to promote the filtering of irrelevant information from important sensory stimuli [59, 60]. Inhibitory gating may not fully mature until adulthood [61], and there is general agreement that inhibitory gating function does not differ between men and women [50; 61, 62, 63, 64].

To assess inhibitory gating function using auditory paired click paradigms, the first click in a pair is commonly identified as the conditioning stimulus (C) and the second click is called the test stimulus (T). The test response is the true evaluation of the inhibitory circuit [51, 56]. The relationship between P50 responses to T and C stimuli can be assessed as a T/C ratio, which is calculated as the test response value divided by the conditioning response value and multiplied by 100 to yield a percentage [62]. The values used in this equation are averaged amplitudes of maximum positive peak (P50) responses occurring within a certain range, such as 40 to 90ms, with a preferred latency near 50ms after stimulus onset [65]. The T/C ratio theoretically represents inhibitory gating function as a value [51]. A low ratio would indicate that the response to the conditioning click is high in amplitude while the response to the test click reduced in comparison. A lower ratio is thought to indicate better inhibitory gating; theoretically, the novel stimulus is attended to while the redundant stimulus is filtered out [60].

A high T/C ratio can be interpreted as impaired inhibitory gating. The cut-off value for normal versus impaired inhibitory gating has been debated, since a high T/C ratio can be the result of different responses patterns. When the test response is higher in amplitude than the conditioning response, as in a T/C ratio over 100, it is possible that a response to stimulus change is being measured rather than inhibitory gating impairment [58]. A recent meta-analysis [65] shows that average ratios for healthy control populations varied from 16% to 94% across various studies, although ratios for schizophrenia patients were higher overall. Chang and colleagues explored if inhibitory gating impairments reflected by T/C ratios were traceable to reduced responses to the conditioning stimulus or an exaggerated response to the test stimulus [65]. It was found that conditioning responses tended to remain stable in healthy controls and in persons with schizophrenia. Thus, responses to novel stimuli did not change. There was great variation in the test response to redundant stimuli in persons with schizophrenia in comparison to healthy controls. This indicates a reduced ability to inhibit or “gate” unnecessary information in schizophrenic patients. This is reflected as similar P50 responses to conditioning and test stimuli.

Reduced or altered responses to the conditioning stimulus may indicate an error in registration rather than inhibitory gating impairment [65]. Therefore, inhibitory gating can be defined as the attenuation of the response to the test stimulus in relation to the conditioning stimulus. Even a very low response to the conditioning stimulus should not be considered a gating problem as long as the T/C ratio is low. It is theoretically possible to have registration and gating problems at once, although they would be indistinguishable in a high T/C ratio. Chang and colleagues suggest a C minus T difference score to supplement interpretations of T/C ratios for this reason.

Emotional influences on P50 inhibitory gating

Early work on psychosis proposed a sensory flooding deficit as a possible factor involved in cognitive and emotional impairment [66, 67, 68]. Inhibitory gating impairment has been observed in persons with emotional impairment including patient samples with schizophrenia, obsessive-compulsive disorder, post-traumatic stress disorder, and Alzheimer’s disease [51, 53, 60, 64, 64, 69, 70, 71, 72]. Inhibitory gating impairments have

been so reliably observed in persons with schizophrenia that P50 has been suggested as a biomarker for diagnosis [73].

There is strong evidence that P50 is a state dependent process since stressors can alter its function. The cold-pressor task is used in human studies to elicit physical stress through the brief induction of pain. The task involves voluntarily keeping one hand in ice water (32–34°F) for several minutes. The cold-pressor is considered safe enough for use in pediatric studies [74]. Johnson and Adler [53] demonstrated that the cold-pressor task can impair inhibitory gating in healthy controls for up to 30 minutes. In this study, the P50 response to the conditioning stimulus was not altered after stress induction, while the response to the test stimulus was heightened in amplitude and caused an increase in T/C ratios. Amplitude and latency remained relatively stable. Half of the participants in the Johnson and Adler study exhibited significantly increased T/C ratios after the cold-pressor task. A later study by Atchley and Cromwell [75] replicated Johnson and Adler's [53] finding that stress caused by the cold-pressor task can transiently impair inhibitory gating in healthy controls.

Mental stressors can also impair inhibitory gating. White and Yee [76] had participants answer arithmetic questions aloud while inhibitory gating responses to auditory clicks were simultaneously recorded. Participants also completed a reaction time task, but the attentional manipulation had no effect on inhibitory gating. The oral arithmetic task was an effective psychological stressor and induced gating impairment so much so that the authors suggested it as a method to model schizophrenia-like gating impairment in healthy persons. Responses to the conditioning and test clicks were reduced for the oral arithmetic task as well as a silent arithmetic task, although results were more pronounced for the oral version. The decrease in the conditioning response from the passive baseline state is noteworthy, as inhibitory gating impairment is usually identified as a diminished test response. However, since the T/C ratios measure the test response relative to the conditioning response, the conclusion of gating impairment is reached. A follow-up study by Yee and White [77] demonstrated that psychological stress induced by a social stressor (prepare to give a speech) or a silent mental arithmetic task also impaired inhibitory gating. The White and Yee [76] finding of stress-related suppression of the P50 response in the oral arithmetic task was replicated. Notably, these stressors only disrupted inhibitory gating when the participants rated the task as anxiety-inducing.

Yee and White [77] considered impaired gating to be the absence of a reduction in response to test stimuli relative to conditioning stimuli. The lack of a reduction is reflected as a higher post-stress T/C ratio in comparison to baseline inhibitory gating. Although the conditioning and test responses were individually sensitive to background noise and sound intensity, the T/C ratios remained constant. Participants listened to a speaking voice in addition to the auditory clicks or performed a silent counting task. The voice task provided auditory competition and successfully disrupted P50 gating. The counting task was a cognitive activity intended to divide attention and distract, but it did not disrupt inhibitory gating unless a participant rated the task as stressful. These findings suggest that competing auditory activity and stress can impair inhibitory gating, while cognitive and attentional manipulations may not. Moreover, the same task may be stressful and cause inhibitory gating impairment in one individual while being innocuous for another individual. There is

individual variation in the experience of stress and its potential to disrupt inhibitory gating [53, 77]. Higher anxiety scores in schizophrenic patients correlate with greater inhibitory gating impairment as well [78], which is further evidence that while gating function may not be disrupted by attention, it may be influenced by mood and emotion.

The P50 component also has potential as a predictive tool. Hutchison and colleagues [79] measured anxious and depressive symptoms in infants, alongside other variables such as attention and externalizing behaviors, which can potentially be linked with behavioral problems. Parents filled out inventories similar to DSM-IV scales when the infants were 70 days old and again when they were 40 months old. Diminished P50 gating at 70 days of age predicted higher anxious and depressive symptoms later on at the 40 months of age. Attentional and externalizing behavioral problems were also predicted by early life P50 gating disruptions. This is strong evidence that gating-related brain abnormalities may be detectable early in life, and that gating impairments in infants may predict later psychopathology.

Emotional influences on gating in the animal model

An investigation into the specific brain regions that show inhibitory gating has been done using recordings from animal models. The amygdala is known to have responses to tones and these responses have been shown to change dependent upon emotional conditioning [80]. We examined responses to short duration tones that were unfamiliar and not associated with any emotional state [81]. We found four main kinds of responses in the amygdala (Figure 3). These included a short duration and long duration excitatory response and a post-stimulus inhibition. We also found an anticipatory response that preceded the tone onset and appeared after the animals had become familiar with the paradigm. All four responses showed significant inhibitory gating with a reduction in the neural activation (or inhibition) to the second stimulus relative to the first. To test the impact of stress on gating in the amygdala, we injected the animals with an isotonic saline injection. Injection with saline has been shown to cause an acute stress reaction [82] and lead to a disruption in sensorimotor gating [83]. The injections impacted all four response types in the amygdala and the main finding was an increased gating for the different responses. The strongest effects were seen in the short-duration excitatory response and in the anticipatory response. This is interesting because these responses could have the most impact on the midlatency component recorded using the ERP scalp technique. The papers on single unit gating have added weight to the idea that the brain pervasively responds to stimuli in rapid and modifiable ways. Would similar responses be found in association cortex? We decided to examine regions of the medial prefrontal cortex in rats and see if short latency auditory responses would be found. Mears and colleagues [84] conducted both local field potential and single unit recording in the medial prefrontal cortex in rats during inhibitory gating. Using the fear conditioning model as a guide, the group decided to take one of the tones used for inhibitory gating and pair it with aversive shocks. The tone-shock conditioning paradigm was adapted from work that examines amygdala neurophysiology [85]. The findings were dramatic in that inhibitory gating weakened in response to tones used in fear conditioning. This effect was seen in multiple components following the auditory stimulus (see Figure 4). To solidify the relationship between gating and aversive tone-shock conditioning, we also found that gating

closely reverted to pre-conditioning levels under extinction. The main idea for the role of prefrontal cortex in the modulation of fear and anxiety is that it sends an inhibitory or regulatory signal to subcortical regions, such as the amygdala [86, 87, 88, 89]. Evidence from human neuroimaging and other animal model work supports this framework and enables predictions for prefrontal cortex functions relative to connected nodes within neural circuits. Previous work has also examined the impact of stress and emotion on gating in the striatum and midbrain regions [90, 91]. A previous review presents data from this work to illustrate how a core function within certain systems like the basal ganglia can intimately depend upon cross-domain integration [92]. The idea that different brain regions must interact for cross-domain communication is rapidly becoming an integral part of behavioral neuroscience research and work on mental illness neuropathology. Even in otherwise healthy persons and rats, inhibitory gating is a susceptible process in that it is influenced by stress and emotional states. Inhibitory gating experiments may help elucidate the roles of cognition and emotion in early processing by parsing out specific factors that can influence or disrupt the gating process.

Inhibitory gating across functional domains

In general terms, sensory processing allows the brain to interpret the outside world via physical sensations. Inhibitory gating can be described as the brain's ability to modulate (or "gate") its responses to incoming sensory stimuli [50]. Theoretically, inhibitory gating allows for irrelevant information to be filtered out in the early stages of sensory processing, thereby promoting more effective cognitive and emotional functioning [59]. Thus, inhibitory gating allows us to effectively adapt to changing environments and attend to relevant information within them. Labeling the mechanism 'sensory gating' may only capture a small piece of the function for these types of early and rapid processes in the brain. It is clear that psychological gating as measured in behavior or neural signals is a top-down modulated phenomenon [35, 93]. A perspective that could be used for future work includes renaming the gating function to offer a wider functional viewpoint. These new labels could include emotional-gating, cognitive gating, or motivational-gating (see Figure 5). Different brain regions would be known to cooperate across a very short time scale using very different information. The filtering of information would be more dependent upon emotional state (primary affects) versus motivational state (sensory affects) and would ultimately be combined as a cross-domain feature for decision making. Since we have found 'anticipatory' gating at the single unit level, it is clear that pre-existing neural states can impact even early neural responses that are time-locked to environmental events [81, 94]. These pre-stimulus expectancies depend heavily on predictability and experience [95]. Existing brain states impact brain oscillations in a strong manner [13]. Buzsaki [13] has argued that different oscillations are spontaneous features of the brain. Moreover, oscillations can enable or disable cognitive function depending upon the temporal relationship of information transfer and the phase of an oscillatory mechanism. Inhibitory gating is triggered by events and relies on sensory input, but it is most likely dependent upon the history of neural information processing and anticipatory states within a network [96]. Recognition of this interaction will allow progress in the understanding of the basic ERPology of gating and the underlying cellular dynamics that span the neuroaxis.

Clinical research and applications are searching for reliable tools in diagnosis, treatment and prevention. The recent push to adopt reliable and valid clinical neurophysiological tools for all of these steps makes the study of cost effective, rapid neurophysiology measures highly significant. For example, researchers demonstrated that inhibitory gating impairments are found in diverse mental illnesses [51, 53, 60, 63, 64, 70, 71, 72, 97]. Previous research has also shown that inhibitory gating has potential as a biomarker and diagnostic tool [73], as well as potential as a developmental predictor of attentional, anxious, and depressive symptomology [79]. It stands to reason that affective factors could likewise influence inhibitory gating function since inhibitory gating is impacted by physical stressors, psychological stressors, and anxiety levels [53, 76, 77, 78]. The wide array of potential influences on inhibitory gating strongly suggests that the process is state dependent. It is an essential next step to translate the neurophysiological techniques and findings in inhibitory gating research to clinical practice. One way to begin thinking about an effective translation is to think along the lines of state or context dependent tests of inhibitory gating that extend the marker beyond baseline or resting levels of gating into the realm of deciphering how well gating is responsive to different perturbations. When the RDocs approach is added to these interactive designs, useful models could arise [98]. This approach could be effective if we understand the normal levels of variability and a typical time window for a return to normal function. The idea could grow into a means to evaluate susceptibilities prior to perturbation and design new avenues for prevention.

This research agenda follows the recent push for common research domains that cross multiple disorders. Testing the integrity of inhibitory gating as it waxes and wanes dependent upon emotional and motivational state functions could be used as a clinical tool across a wide range of mental illnesses. The common feature among the set of illnesses would be a dysfunction in gating that would be indicated as a breakdown in the ability to process information while competing or new information is experienced. The sort of information processing functions and the nature of the vulnerability might be different depending upon the mental disorder but these same diverse illnesses could share a commonality in disrupted gating function. Future work could focus on pinpointing the shared nature of gating impairments in order to further understand the common thread that combines different mental illnesses, and additional research should extend this work to design ways to protect inhibitory gating mechanisms and associated psychological processes.

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Highlights

- Inhibition is a global and local brain process
- Measuring inhibition in psychology has focused on cognition or emotion
- A better method could be measuring an interaction between emotion and cognition
- Recent work has shown value in this cross-domain approach
- Future work can profit by combining measures and examining interactive processing

Figure 1.

Histograms of USV emission for the 3 different sessions that vary in terms of predictability.

A) This session replicated previous work using a variable interval (VI) schedule of trial delivery. Trials came at a VI = 12.5 s and trials included loud tone (PA), PPI (loud tone preceded by soft tone) and PP (soft tone alone). The timing and trial types were unpredictable. USVs rise gradually and then are maintained consistently throughout the session. USVs were seen consistently across all three trial types. B) This session (FI) used a fixed interval (15 s) between each trial. PPI did not change even with high predictability of timing for the trials. USVs were not reduced and slightly increased across all trials. C) Fixed interval and blocked session included highest predictability with 15 s FI along with blocks of trial types. The order of presentation made significant difference. In this example the soft tone trials do not elicit calls since they are at the session start. When at the end, the same PP block does lead to USV calling, as a generalization to the aroused and aversive state the animals have experienced with the repetitive loud tones (modified from Ref. [41]).

Figure 2.

An example of a local field potential recorded from a single wire yields waveforms for both tones in a paired-comparison block of trials. A P60 occurred as a positive going peak 60 milliseconds after the first tone (C_{tone}) at 0 seconds. Another P60 occurred at 60 milliseconds after the second tone (T_{tone}) at 0.5 sec. Gating of the second tone is apparent in the diminished amplitude of P60 when compared to P60 following the first tone (modified from Ref. [19]).

Figure 3.

We examined inhibitory gating by recording from neurons in the amygdala. Four different types of single unit responses were found in this limbic brain region. A) Excitatory response-short duration gating (E-SD). This response is a very brief increase in activity following the initial, conditioning tone. The increase in activity related to the tone response is completely absent from the test tone 2. B) Excitatory response-long duration (E-LD). This response was a sustained increase in activity following the test stimulus. In some cases, the increase in activity was prolonged through the onset of the conditioning stimulus 500 ms later. C) An example of anticipatory gating. A select set of cells showed this gradual activity increase prior to the initial tone that was absent prior to the second tone in the pair. D) An example of inverse gating (Inh). Some neurons showed an inhibition following the test stimulus that was significantly reduced at the time of the conditioning stimulus (modified from Ref [81]). The tone related activations are not consistently seen throughout a gating session but arise in clusters interspersed with reduced or absence activity to the stimulus. We

explored this periodicity by examining whether or not responses to the stimuli were influenced by active movement (see Ref [84]). In most cases, the tone responses were dampened when the animal was active and intentional movement could be an important factor leading to the reduction or absence of the tone-related activity in certain sets of trials (e.g., during locomotion or grooming).

Figure 4.

Waveforms are representative of medial prefrontal cortex local field potential responses recorded from the same microelectrode during inhibitory gating. T/C ratios indicate the proportional relationships for each auditory evoked potential component in response to the initial or conditioning tone (C; black trace) and the second or test tone (T; gray trace) in Before (A), After conditioning (B), and Extinction sessions (modified from Ref. [19]).

Figure 5.

Forebrain areas are potentially involved in various types of gating depending on the region and type of inhibition. Forebrain regions involved in cognitive gating include the cortex for executive function and decision making, and the hippocampus for short-term and working memory. Motivation gating in the striatum influences reward seeking behavior. Emotional gating in the amygdala plays a role in emotion regulation. The thalamus is involved in sensory gating and relays this information to forebrain areas. Likewise, networks in the midbrain, hindbrain, and spinal cord rely on central nervous system sensory gating via inhibition at every level.