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Research report

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

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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.

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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.

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 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

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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 over-simplified 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 [6–8]. 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.

1. 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.

2. Psychological gating and sensorimotor reflexes

One way that inhibitory processes are often studied is by monitoring the primitive startle reflex [24,25]. 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