REVIEW

THE APPLICATION OF ERP PARADIGMS IN CLINICAL AND NON-CLINICAL RESEARCH

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ABSTRACT

This comprehensive review paper examines the utilization of Event-Related Potentials (ERPs) in both clinical and non-clinical research. ERPs serve as valuable electrophysiological measures for studying neural activity associated with cognitive processes, offering high temporal accuracy and noninvasive observation of brain responses. The paper explores the benefits, challenges, and limitations of employing ERP paradigms in research. Technical expertise is necessary due to factors such as low signal-to-noise ratio and potential artifacts. These limitations must be addressed to ensure robust experimental design and accurate interpretation of findings. The review investigates the diverse applications of ERPs in clinical research, particularly in neurological and psychiatric conditions, where ERPs contribute to understanding underlying neural mechanisms and potential biomarkers. Additionally, non-clinical research areas, such as language processing and attentional mechanisms, are examined for their insights into cognitive processes. The current state of the field is discussed, with a focus on potential future directions. Technological advancements, including signal processing techniques, electrode design, and data analysis methods, are identified as areas for further development to improve the reliability and ease of use of ERP paradigms. It generally highlights the significance of ERPs as a powerful tool in cognitive neuroscience research. By examining their applications, challenges, and future prospects, the paper emphasizes the need for continued technological advancements to fully unlock the potential of ERPs in both research and clinical settings.

Keywords: *"Event-Related Potentials (ERPs)", "clinical research", "non-clinical research", "neural activity", "mental processes", "noninvasive technique"*

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INTRODUCTION

Event-Related Potentials (ERPs) have emerged as a potent means of assessing and evaluating neural activity associated with mental processes in both clinical and non-clinical research (1). This electroencephalography (EEG) method enables the recording of electrical signals produced by the brain in response to a specific stimulus that can be used to analyze the timing and location of cognitive functions (2, 3, 4). ERP paradigms offer a noninvasive technique for observing brain activity with high temporal accuracy (5).

Within the field of clinical research, ERPs have been extensively utilized to gain insights into various neurological and psychiatric conditions, including autism spectrum disorder (6, 7), developmental dyslexia (6, 8), and obsessive-compulsive disorder (6, 9). Additionally, in non-clinical studies, ERPs have been employed to investigate language (6, 10) and attentional processing (11). ERPs can be categorized into two groups based on their timing (14, 12). The early waves, occurring within the first 100 milliseconds, depend mostly on the physical characteristics of the stimulus and are called 'sensory' or 'exogenous' components (14, 12). The later waves, reflecting the subject's processing of the stimulus, are known as 'cognitive' or 'endogenous' components (14, 12).

Despite its various advantages, using ERP paradigms has some limitations. One of the most important is its complex technicality, which requires specialized technology and proficiency to set up and interpret data, both of which can be costly and tedious (6). Additionally, the signal-to-noise ratio of ERP paradigms is usually low, resulting in difficulties in precisely measuring changes in brain activity (6).

ERPs, characterized by high temporal resolution and sensitivity to subtle changes in cognitive processing (15), have the advantage of distinguishing between different components of neural activity that occur in response to a stimulus, enabling more precise measurements of cognitive function (16). However, ensuring that the measured electrical activity is related to the specific cognitive process under investigation requires a careful experimental design (5). Additionally, collecting and analyzing ERP data require specialized equipment and expertise, which can be time-consuming and costly (11). The low signal-to-noise ratio of ERP paradigms further poses challenges (17).

Despite these limitations, ERP paradigms have gained popularity in both clinical and non-clinical research. In the following sections, we explore some of the ways in which ERP paradigms are utilized in these two domains, highlighting their distinct contributions and limitations (6, 12)

This study aims to provide a comprehensive overview of the utilization of ERP paradigms in clinical and non-clinical research. It will explore the benefits, difficulties, and restrictions of using ERP paradigms in research, as well as the current state and potential future

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directions of the field.

APPLICATIONS OF ERP PARADIGMS IN CLINICAL RESEARCH

ERP paradigms have been used in a wide range of clinical research contexts to provide valuable insights into the neural underpinnings of cognitive and behavioral deficits in various neurological and psychiatric disorders (18, 19). Some key applications of ERP paradigms in clinical research are outlined below.

Measuring Cognitive Function in Neurological Disorders

ERP paradigms have been used extensively in research on neurological disorders, such as autism spectrum disorder (ASD) (20), Schizophrenia (21), Attention-deficit/hyperactivity disorder (ADHD) (22), Major depressive disorder (MDD) (23), Alzheimer's disease (24), Parkinson's disease (25), obsessive-compulsive disorder (OCD) (26), Multiple sclerosis (MS) (27), bipolar disorder (28), Traumatic brain injury (TBI) and Epilepsy (29).

In these studies, researchers used ERP measurements to investigate changes in cognitive function (12, 30), including attention, memory, and language processing. For example, studies have shown that patients with Alzheimer's disease have reduced P300 amplitudes and longer P300 latencies than healthy controls, indicating deficits in working memory and attention (30).

ERP paradigms have been extensively used in clinical research to investigate the cognitive processes underlying various neurological and psychiatric disorders (11). These paradigms are used to record the electrical activity of the brain in response to specific stimuli, thereby providing insights into the neural processes that underlie cognitive functions. One of the significant advantages of ERP paradigms is their high temporal resolution, which allows researchers to track changes in brain activity with millisecond precision (5). Some ERP uses in neurological disorders are explained below.

i. ERP Paradigms in Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder that primarily affects memory and cognitive functions (31). ERPs are widely used to investigate cognitive processes in patients with AD (32). Several ERP paradigms have been used in AD research, including the oddball paradigm (33), the P300 paradigm (32), and the N400 paradigm (34).

The oddball paradigm is a simple auditory task that involves presenting a series of standard stimuli (frequent tones) and infrequent deviant stimuli (rare tones) to the participant. The paradigm measures the processing of deviant stimuli, as reflected in the mismatch negativity (MMN) component of the ERP waveform (35). The MMN is a negative deflection that occurs around 100-250 ms after the deviant stimulus onset and is thought to reflect the automatic detection of changes in auditory stimuli. Several studies have shown that patients with AD exhibit reduced MMN

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amplitudes, suggesting impaired auditory processing (35, 36, 37).

The P300 paradigm is another widely used ERP paradigm in AD research32. The P300 is a positive deflection that occurs around 300-500 ms after the presentation of an infrequent stimulus and is thought to reflect attention and memory processes (38). Several studies have found that patients with AD exhibit reduced P300 amplitudes and prolonged latencies, suggesting deficits in attention and memory processes (38, 39, 40).

The N400 is a negative deflection that occurs around 300-500ms after the presentation of a semantic violation. It is an event-related potential (ERP) component that is part of the N400 paradigm, which is used to investigate semantic processing. The N400 paradigm involves presenting a subject with a series of words or sentences, some of which contain a semantic violation or mismatch (e.g., "He spread the warm bread with socks"). Several studies have found that patients with Alzheimer's disease (AD) exhibit reduced N400 amplitudes and prolonged latencies, suggesting deficits in semantic processing (41,42).

ii. ERP Paradigms in Epilepsy

ERP studies have been utilized to investigate cognitive processes in patients with epilepsy, a neurological disorder characterized by recurrent seizures (43, 44). Several studies have found that patients with epilepsy exhibit deficits in several cognitive processes, including attention (45), memory (46), and language processing (46), as reflected in their ERP responses. One commonly used ERP paradigm in epilepsy research is the oddball paradigm, which involves presenting infrequent target stimuli in a sequence of frequent non-target stimuli to elicit a P300 response, a component thought to reflect cognitive processes such as attention and working memory (47).

(48, 49) found that patients with schizophrenia and epilepsy exhibited reduced P300 amplitudes during an auditory verbal hallucination task, suggesting a deficit in attention and working memory. Another study by (50) found that patients with epilepsy showed abnormal P600 responses, which are thought to reflect syntactic processing during language comprehension.

Furthermore, studies have demonstrated that patients with epilepsy also exhibit abnormalities in the N400 component, which reflects semantic processing during language comprehension (51, 52). Specifically, (47) found that children with epilepsy exhibited a reduced N400 response during the observation of repeating visual stimuli, indicating difficulties in processing semantic information.

iii.ERP Paradigms in Schizophrenia

Schizophrenia is a severe mental disorder that affects around 1% of the population worldwide (53) approximately 20 million people worldwide (54). It is characterized by a range of cognitive, emotional, and behavioral symptoms, including hallucinations, delusions, disorganized thinking, and social withdrawal

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(55, 56). ERP paradigms have been widely used in schizophrenia research to investigate cognitive processes and neural mechanisms underlying these symptoms (4, 57).

The N1 component is an event-related potential (ERP) that reflects early sensory processing of auditory stimuli. It is one of the most consistent ERP findings in schizophrenia, with patients exhibiting a significant reduction in N1 amplitude across a variety of auditory paradigms. This reduction in N1 amplitude has been suggested to reflect deficits in sensory gating, which is the ability of the brain to filter out irrelevant stimuli. A meta-analysis by (58) found that patients with schizophrenia exhibited a significant reduction in N1 amplitude, providing further evidence for the role of N1 in the pathophysiology of schizophrenia (59, 60, 61).

Another widely studied ERP component in schizophrenia is the P300, which is thought to reflect attention and working memory processes (62). Several studies have reported reduced P300 amplitude and delayed latency in patients with schizophrenia compared to healthy controls (33, 62, 63). This deficit in P300 has been associated with cognitive impairments in patients with schizophrenia, such as deficits in attention and working memory (33, 62).

ERP studies have also examined other cognitive processes in schizophrenia, such as semantic processing and language comprehension. A study by (64) found that patients with schizophrenia showed reduced N400 amplitude, an ERP component that reflects semantic processing during language comprehension. This deficit in N400 amplitude has been suggested to reflect impairments in semantic memory in patients with schizophrenia (65).

In addition to these ERP findings, studies have also explored the potential use of ERP measures as biomarkers for schizophrenia diagnosis and treatment response (66, 67). For example, a study by (68) found that P300 amplitude could distinguish between patients with schizophrenia and healthy controls with high accuracy, suggesting its potential use as a diagnostic tool. Another study by (69) found that P300 amplitude could predict treatment response in patients with schizophrenia, suggesting its potential use as a biomarker for treatment monitoring.

Tracking Changes in Brain Activity after a Traumatic Event

ERP paradigms have been widely used to investigate the impact of traumatic events on brain activity, particularly in individuals who develop post-traumatic stress disorder (PTSD) (70). PTSD is a mental disorder that can develop after exposure to a traumatic event, such as physical or sexual assault, combat, or natural disasters (56). Individuals with PTSD may experience symptoms such as flashbacks, nightmares, avoidance of triggers, and heightened emotional reactivity (71).

One area of research using ERP paradigms in PTSD has

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focused on emotional processing (72). Several studies have found that individuals with PTSD show reduced P300 amplitudes and longer latencies when processing emotionally charged stimuli, such as images of combat or trauma-related words (72,73). The P300 is an ERP component that reflects the attention and working memory processes, and its reduction in individuals with PTSD has been suggested to reflect deficits in the cognitive processing of emotional stimuli (72,74).

Another area of research using ERP paradigms in PTSD has focused on cognitive control processes. Studies have found that individuals with PTSD exhibit deficits in inhibitory control and response monitoring, as reflected in their reduced N2 and error-related negativity (ERN) amplitudes (75,76). The N2 is an ERP component that reflects attentional and inhibitory control processes, while the ERN is an ERP component that reflects error detection and response monitoring. These deficits in cognitive control processes have been suggested to contribute to the intrusive thoughts and hypervigilance symptoms commonly observed in individuals with PTSD (77).

In addition to emotional processing and cognitive control processes, ERP paradigms have also been used to investigate memory processes in PTSD. Studies have found that individuals with PTSD exhibit deficits in memory retrieval, as reflected in their reduced N400 amplitudes during memory recall tasks (78). The N400 is an ERP component that reflects semantic processing during language comprehension and memory retrieval tasks (78).

Advantages and Limitations of Using ERP Paradigms in Clinical Research

ERP paradigms offer several advantages for clinical research, including their ability to measure specific cognitive processes with high temporal resolution (5). They also provide a non-invasive and relatively inexpensive way to investigate changes in brain activity over time (79). However, there are also limitations to using ERP paradigms in clinical research, including the need for careful experimental design to ensure that the measured electrical activity is related to the specific cognitive process of interest. Additionally, ERP measurements can be affected by factors such as medication use and comorbidities, which can complicate the interpretation of results (80). ERP has a low signal-to-noise ratio, which means that the signal of interest is often buried in noise5. ERP is also limited in its ability to localize the neural generators of the ERP components (81). Finally, ERP is limited in its ability to measure the activity of deep brain structures (82).

Overall, ERP paradigms have shown promise as a tool for investigating cognitive function in neurological and psychiatric disorders. While there are some limitations to using ERP paradigms in clinical research, they offer a valuable way to investigate changes in brain activity over time and may have the potential for developing diagnostic or treatment approaches (83).

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APPLICATION OF ERP PARADIGMS IN NON-CLINICAL APPLICATION

In addition to their use in clinical research, ERP paradigms have been used extensively in non-clinical research to investigate various cognitive processes, including attention, perception, memory, decision-making, and language processing (5). Some of the key applications of ERP paradigms in non-clinical research are outlined below:

i. Language Processing

ERP paradigms have been used extensively in research on language processing, providing insights into the neural underpinnings of various linguistic processes (84). For example, studies have used ERP measurements to investigate how the brain processes different aspects of language, such as syntax, semantics, and pragmatics (85). One commonly used paradigm is the N400, which is a negative-going waveform that is elicited by semantic violations in sentences (10, 85).

A study by (86) used the semantic anomaly paradigm and found that the amplitude of the N400 component is larger when participants are presented with semantically anomalous sentences compared to semantically congruent sentences. This finding suggests that the N400 component reflects the neural processing of semantic information. Another study by (87) used the syntax violation paradigm and found that the amplitude of the P600 component is larger when participants are presented with syntactically violated sentences compared to syntactically congruent sentences, suggesting that the P600 component reflects the neural processing of syntactic information.

ii. Attentional Processing

ERP paradigms have also been used to investigate attentional processing, including how attention is allocated to different stimuli and how it is maintained over time. For example, studies have used ERP measurements to investigate how the brain processes visual and auditory stimuli, showing that different ERP components are associated with different aspects of attentional processing (5). studies have used the oddball paradigm to investigate the neural mechanisms underlying attentional allocation and have found that the amplitude of the P3 component is larger for attended stimuli compared to unattended stimuli (88). Another study by (89) used the visual search paradigm and found that the amplitude of the N2 component is larger when participants are searching for a target compared to when they are not.

ERP paradigms have also been used to investigate the neural mechanisms underlying perceptual processes. A study by (90) used the visual paired comparison paradigm and found that the amplitude of the P1 component is larger when participants are presented with stimuli that are physically different compared to when they are presented with identical stimuli. This finding suggests that the P1 component reflects the neural processing of physical differences between

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stimuli.

The N2 component is an event-related potential (ERP) that is typically elicited in response to cognitive processes involved in attention and decision-making. In the visual search paradigm, the amplitude of the N2 component has been found to be larger when participants are searching for a target compared to when they are not, as demonstrated in a study by (89). This suggests that the N2 component is involved in the processing of task-relevant information during visual search tasks.

iii.Decision Making

ERP paradigms have also been used to investigate cognitive processes involved in decision-making. For example, studies have used ERP paradigms to investigate the neural processes underlying decision-making in various contexts, such as economic decision-making and moral decision-making (91, 92). A study by (93) investigated the neural processes underlying decision-making in a gambling task using an ERP paradigm. They found that participants showed a distinct pattern of ERP responses to winning versus losing outcomes, suggesting that the neural processes underlying decision-making could be identified with ERPs.

Another study by (94) used the ultimatum game paradigm and found that the amplitude of the feedback-related negativity (FRN) component is larger when participants receive unfair offers compared to fair offers. Their finding suggests that the FRN component reflects the neural processing of feedback that violates expectations. The study by (95) used the gambling task paradigm and found that the amplitude of the FRN component is larger when participants make risky decisions compared to safe decisions, suggesting that the FRN component reflects the neural processing of risk.

iv. Memory Processing

ERP paradigms have been extensively used to investigate the neural mechanisms underlying memory processes. The recognition memory paradigm, in which participants are presented with a series of stimuli and are later asked to recognize whether they have seen those stimuli before or not, has been widely used in ERP studies of memory (96,97). One of the most consistent findings in this paradigm is the old/new effect, a positive deflection in the ERP waveform that occurs when participants correctly recognize an old stimulus as old, compared to when they correctly reject a new stimulus as new (98). This effect has been shown to reflect the neural processing of memory retrieval, with the amplitude of the old/new effect being larger for correctly recognized items compared to incorrectly recognized items (96, 98).

Another important ERP paradigm used to investigate memory processes is the recollection/familiarity paradigm, in which participants are presented with a series of stimuli and are later asked to indicate whether they recollect or simply recognize those stimuli (99). The parietal old/new effect, a positive deflection in the

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ERP waveform that occurs around 500 ms after stimulus presentation, has been shown to reflect the neural processing of recollection, the conscious retrieval of detailed contextual information associated with a past event (100). Specifically, the amplitude of the parietal old/new effect has been found to be larger for recollected items compared to familiar items, suggesting that this effect is a reliable neural marker of recollection (100).

In addition to these findings, ERP studies have also investigated the neural mechanisms underlying other memory processes, such as working memory and source memory (100). For example, studies have found that the P300 component of the ERP waveform is sensitive to working memory load, with larger P300 amplitudes observed for high-load compared to low-load working memory tasks (101). Other studies have investigated the neural mechanisms underlying source memory, the ability to remember the context in which a memory was formed (102). These studies have found that the ERP waveform contains a late positive component, the so-called "retrieval success effect", which is sensitive to source memory and reflects the neural processing of source retrieval (102).

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Advantages and Limitations of Using ERP Paradigms in Non-Clinical Research

ERP paradigms offer several advantages for non-clinical research, including their ability to measure specific cognitive processes with high temporal resolution. ERP measurements can be affected by factors such as participant age and individual differences in cognitive abilities, which can complicate the interpretation of results (80).

Overall, ERP paradigms have shown promise as a tool for investigating cognitive processes in non-clinical research. While there are some limitations to using ERP paradigms in non-clinical research, they offer a valuable way to investigate changes in brain activity over time and may have the potential for developing theoretical models of cognitive processes.

Despite these differences, ERP paradigms remain a valuable tool for investigating cognitive processes in both clinical and non-clinical research (5). They provide insights into the underlying neural mechanisms of cognitive processes and can contribute to the development of diagnostic and treatment approaches for neurological and psychiatric disorders (105).

CHALLENGES AND FUTURE DIRECTION

While ERP paradigms offer several advantages for investigating cognitive processes, there are also several challenges associated with their use. One of the primary challenges is the variability in the ERP signal due to factors such as individual differences in neural activity and noise in the recording environment (5). This variability can make it challenging to detect reliable effects and generalize findings across participants and tasks (5).

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Another challenge is the difficulty in interpreting the meaning of the ERP signal. The ERP waveform is composed of several components, each of which is associated with a specific cognitive process, and the interpretation of these components can be complex (5). Additionally, ERP studies typically involve the use of multiple electrodes, and the interpretation of the results can be influenced by the selection of electrodes and the methods used to analyze the data (106).

Despite these challenges, ERP paradigms continue to be a valuable tool for investigating cognitive processes. Future directions for research using ERP paradigms include the development of new methods for analyzing ERP data and the integration of ERP data with other neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), to provide a more comprehensive understanding of the neural processes underlying cognitive function (107).

Another future direction is the use of ERP paradigms in clinical populations to investigate the neural processes underlying cognitive dysfunction in disorders such as schizophrenia, depression, and anxiety (108). By investigating the neural mechanisms underlying cognitive dysfunction in clinical populations, ERP paradigms have the potential to inform the development of new interventions and treatments for these disorders (108).

CONCLUSION

ERP paradigms have become increasingly popular in both clinical and non-clinical research, offering a valuable tool for investigating cognitive processes with high temporal resolution. In clinical research, ERP paradigms have been used to investigate various neurological and psychiatric disorders, providing insights into the neural underpinnings of cognitive and behavioral deficits and helping to develop diagnostic and treatment approaches. In non-clinical research, ERP paradigms have been used to investigate theoretical models of cognitive processes, providing insights into how the brain processes information.

While there are some differences in the use of ERP paradigms in clinical and non-clinical research, they share many similarities in terms of experimental design and interpretation of results. Overall, ERP paradigms offer a valuable way to investigate changes in brain activity over time, and may have the potential to advance our understanding of cognitive processes in both clinical and non-clinical contexts.

Looking forward, there is still much to be learned about the potential applications of ERP paradigms in both clinical and non-clinical research. Ongoing technological advancements and the development of new analytic techniques hold great promise for furthering our understanding of the neural underpinnings of cognitive processes and developing new diagnostic and treatment approaches for various

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neurological and psychiatric disorders, the integration of ERP data with other neuroimaging techniques, and the use of ERP paradigms in clinical populations to investigate the neural mechanisms underlying cognitive dysfunction. As such, ERP paradigms are likely to remain a valuable tool in cognitive neuroscience research for many years to come.

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Table I: Measuring Cognitive Function in Neurological Disorders

Neurological Disorder	Focus of Investigation	Author(s)
Autism spectrum disorder (ASD)	Attention and emotion processing	(20)
Schizophrenia	Sensory and cognitive processing	(21)
Attention-deficit/hyperactivity disorder (ADHD)	Attention and cognitive control	(22)
Major depressive disorder (MDD)	Emotional processing and cognitive control	(23)
Alzheimer's disease	Cognitive decline and memory impairment	(24)
Parkinson's disease	Motor and cognitive deficits	(25)
Obsessive-compulsive	Cognitive control and response	(26)

disorder (OCD)	inhibition	
Multiple sclerosis (MS)	Cognitive impairment and sensory processing	(27)
Bipolar disorder	Emotional processing and cognitive control	(28)
Traumatic brain injury (TBI)	Cognitive impairment and sensory processing	(29)
Epilepsy	Sensory and cognitive processing, seizure activity	(29)

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Table II: Comparison of ERP Paradigm in Clinical and non-clinical Research (103, 5, 11, 104)

Aspect	Clinical Research	Non-Clinical Research
Goals of Research	Clinical research aims to investigate the neural mechanisms underlying cognitive and behavioral impairments in neurological and psychiatric disorders	Non-clinical research aims to explore theoretical models of cognitive processes and the underlying neural mechanisms in healthy individuals, with the aim of advancing our understanding of how the brain processes information
Participant Characteristics	In clinical studies, researchers must take into account a wide range of individual differences and clinical variables that may affect the results, such as medication use, symptom severity, and comorbid conditions.	In non-clinical studies, researchers have more control over experimental variables and can manipulate them in a more systematic and controlled manner to test specific hypotheses.
Experimental Design	Clinical research requires a more cautious approach due to the influence of medication use and comorbidities on participants' responses, requiring researchers to carefully match participants.	Non-clinical research focuses on manipulating cognitive processes to examine how they reflect in the ERP waveform
Interpretation of Results	Clinical research focuses on identifying abnormal patterns of ERP activity that are associated with specific neurological or psychiatric disorders, with the goal of developing diagnostic or treatment approaches.	Non-clinical research uses ERP data to identify theoretical models of cognitive processes

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