Universidade Federal do Pará
Núcleo de Teoria e Pesquisa do Comportamento
Programa de Pós-Graduação em Neurociências e Comportamento

A relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo na epilepsia: Uma revisão sistemática e meta-análise

Iris do Carmo Leite

BELÉM – PA

2026

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A RELAÇÃO ENTRE OS PARÂMETROS DO POTENCIAL EVOCADO P300 E O COMPROMETIMENTO COGNITIVO NA EPILEPSIA: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

Dissertação apresentada ao Programa de Pós-Graduação em Neurociência e Comportamento, do Núcleo de Teoria e Pesquisa da Universidade Federal do Pará, como parte dos requisitos para obtenção do título de Mestre em Neurociências e Comportamento.

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BELÉM – PA

2026

Dados Internacionais de Catalogação na Publicação (CIP)
UFPA/Núcleo de Teoria e Pesquisa do Comportamento/Biblioteca

L533r Leite, Iris do Carmo, 1988-
A relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo na epilepsia: uma revisão sistemática e meta-análise / Iris do Carmo Leite. — 2026.
67 f.: il.

Orientadora: Silene Maria Araújo de Lima
Coorientador: Fernando Allan de Farias Rocha
Dissertação (Mestrado) - Universidade Federal do Pará, Núcleo de Teoria e Pesquisa do Comportamento, Programa de Pós- Graduação em Neurociências e Comportamento, Belém, 2026.

1. Análise do comportamento. 2. P300 (avaliação neurofisiológica). 3. Epilepsia (doença neurológica). 4. Comprometimento cognitivo. 5. Revisão sistemática. I. Título.

CDD - 23. ed. — 616.83

Catalogação na fonte: Maria Célia Santana da Silva – CRB2/780

O presente trabalho foi realizado com apoio da Fundação Amazônia de Amparo a Estudos e Pesquisa e da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil.

This study was financed in part by the Fundação Amazônia de Amparo a Estudos e Pesquisa Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil.

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Data da Aprovação: 26/03/2026

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Título do Trabalho: A relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo na epilepsia: Uma revisão sistemática e meta-análise.
Data da Defesa: 26/03 /2026 Área do Conhecimento: Ciências Biológicas
Linha de Pesquisa: Processos comportamentais complexos
Agência de Fomento: FAPESPA *Para cada autor, uma autorização preenchida e assinada.

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Agradecimentos

Agradeço, antes de tudo, às minhas filhas, Iohana e Poliana, que foram minha maior inspiração e razão para seguir em frente mesmo nos momentos mais difíceis. Cada sorriso, cada abraço, cada olhar de amor me deu forças para persistir quando o cansaço parecia maior que eu. Este trabalho é também de vocês, porque me ensinaram todos os dias o verdadeiro significado de coragem e resiliência.

Reconheço que o caminho até aqui não foi fácil. Enfrentei obstáculos pessoais, lutas internas e externas, e precisei me reinventar inúmeras vezes. Mas foi nesse processo que encontrei crescimento, amadurecimento e a certeza de que cada desafio me tornou mais forte.

À minha família, que me apoiou nos momentos em que pensei não conseguir, meu mais profundo agradecimento. Em especial à minha mãe, pelo exemplo de força e amor incondicional, e a todos que acreditaram em mim quando eu mesma duvidei.

Ao meu pai, (in memoriam), dedico esta conquista com todo meu amor. Sei que, do outro lado, ele torce por mim e vibra com cada passo dado nesta caminhada. Sua presença permanece viva em minhas memórias e em meu coração.

Aos meus orientadores, Prof. Fernando Allan Rocha e Profa. Silene Maria Araújo de Lima, minha gratidão pela paciência, pela confiança e pelas orientações que me guiaram. Aprendi não apenas ciência, mas também a importância da ética, da disciplina e da paixão pela pesquisa.

A todos os professores do Núcleo de Teoria e Pesquisa do Comportamento, agradeço imensamente pelas contribuições, ensinamentos e inspirações que, de diferentes formas, marcaram minha trajetória.

À FAPESPA, pela concessão da bolsa de estudos que viabilizou esta pesquisa, meu sincero reconhecimento e agradecimento.

Dedico também esta conquista a todas as mulheres ancestrais da minha família que sonharam com este momento, mas não puderam vivê-lo. Carrego cada uma de vocês em mim, e é com profundo respeito e gratidão que partilho este caminho, que não começou comigo e não termina aqui.

Aos amigos e colegas que dividiram comigo angústias, cafés, risadas e incentivos, obrigada por caminharem ao meu lado.

E, por fim, agradeço aos Deuses, em todas as suas formas e manifestações, pela inspiração, pela força e pela luz que me acompanharam nesta jornada. Sem essa espiritualidade, eu não teria encontrado equilíbrio para seguir adiante.

Minha eterna gratidão,

Iris do Carmo Leite

“A primeira e maior das vitórias é conquistar a si mesmo.

Coragem é uma espécie de salvação.

Coragem é saber o que não temer.”

— Platão / Inspiração em *My Salvation*, Sakis Tolis

Leite, I. do C. (2026). A relação entre os parâmetros do Potencial Evocado P300 e o comprometimento cognitivo na epilepsia: Uma Revisão Sistemática e Meta-análise. Dissertação de Mestrado. Programa de Pós-Graduação em Neurociências e Comportamento, Universidade Federal do Pará – UFPA, Belém, PA, Brasil. 67p.

RESUMO

Resumo: A epilepsia é um distúrbio neurológico crônico frequentemente associado a alterações cognitivas que afetam domínios como atenção, memória e velocidade de processamento da informação, impactando significativamente a qualidade de vida dos indivíduos. Nesse contexto, o potencial evocado P300, obtido por meio do eletroencefalograma, tem sido amplamente utilizado como medida eletrofisiológica objetiva para investigar desempenho cognitivo em indivíduos com epilepsia. **Objetivos:** Analisar a relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo em indivíduos com epilepsia, por meio de uma revisão sistemática da literatura. **Metodologia:** Realizou-se revisão sistemática conduzida conforme as diretrizes PRISMA, com busca nas bases PubMed e LILACS entre janeiro de 2020 e junho de 2025. A seleção dos estudos foi conduzida por dois revisores independentes. Foram incluídos estudos observacionais e ensaios clínicos que avaliaram parâmetros do P300 associados ao desempenho cognitivo em indivíduos com epilepsia. A qualidade metodológica foi avaliada pela escala Newcastle–Ottawa (NOS). Quando disponíveis dados quantitativos comparáveis, realizou-se meta-análise da latência do P300, utilizando diferenças médias padronizadas (SMD) sob modelo de efeitos aleatórios com estimador Restricted Maximum Likelihood (REML). Devido à heterogeneidade dos instrumentos cognitivos e da forma de reporte estatístico, as associações entre parâmetros do P300 e domínios cognitivos foram adicionalmente sintetizadas por meio de síntese integrativa estruturada dos achados. **Resultados:** Dez estudos foram incluídos na síntese qualitativa. Os escores da NOS variaram entre 5 e 9 estrelas, com limitação recorrente no domínio de comparabilidade. Quatro estudos forneceram dados suficientes para a meta-análise da latência do P300. A estimativa combinada sob modelo de efeitos aleatórios demonstrou prolongamento estatisticamente significativo da latência em indivíduos com epilepsia em comparação a controles (SMD = 1,29; IC 95%: 1,03–1,54; $p < 0,001$), sem evidência de heterogeneidade estatística ($I^2 = 0\%$; $\tau^2 = 0,00$; $Q(3) = 2,01$; $p = 0,57$). Testes de viés de publicação não indicaram assimetria significativa (Begg $p = 0,333$; Egger $p = 0,303$), embora o número reduzido de estudos limite o poder estatístico. Na síntese integrativa dos achados, o prolongamento da latência foi mais frequentemente associado a pior desempenho em cognição global, atenção, velocidade de processamento e funções executivas. A redução da amplitude esteve associada a prejuízos em atenção, funções executivas e memória de trabalho. Subgrupos com maior gravidade clínica, incluindo epilepsia farmacorresistente e politerapia, apresentaram alterações combinadas de latência prolongada e amplitude reduzida acompanhadas de pior desempenho cognitivo. **Conclusão:** As evidências indicam que o P300 é um marcador eletrofisiológico sensível do comprometimento cognitivo na epilepsia, refletindo características clínicas da doença e os efeitos do tratamento, com potencial aplicação complementar à avaliação neuropsicológica.

Palavras-chave: Epilepsia; P300; Comprometimento cognitivo; Revisão sistemática.

Leite, I. do C. (2026). The Relationship between P300 Evoked Potential parameters and Cognitive Impairment in Epilepsy: A Systematic Review and Meta-Analysis. Master's Dissertation. Graduate Program in Neurosciences and Behavior, Federal University of Pará – UFPA, Belém, PA, Brazil. 67 pages.

ABSTRACT

Abstract: Epilepsy is a chronic neurological disorder frequently associated with cognitive alterations affecting domains such as attention, memory, and information processing speed, significantly impacting the quality of life of individuals. In this context, the P300 evoked potential, obtained through electroencephalography, has been widely used as an objective electrophysiological measure to investigate cognitive performance in individuals with epilepsy. **Objectives:** To analyze the relationship between P300 evoked potential parameters and cognitive impairment in individuals with epilepsy, through a systematic literature review. **Methodology:** A systematic review was conducted according to the PRISMA guidelines, searching the PubMed and LILACS databases between January 2020 and June 2025. Study selection was conducted by two independent reviewers. Observational studies and clinical trials that evaluated P300 parameters associated with cognitive performance in individuals with epilepsy were included. Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS). When comparable quantitative data were available, a meta-analysis of P300 latency was performed using standardized mean differences (SMD) under a random-effects model with a Restricted Maximum Likelihood (REML) estimator. Due to the heterogeneity of cognitive instruments and the form of statistical reporting, the associations between P300 parameters and cognitive domains were additionally synthesized through a structured integrative synthesis of the findings. **Results:** Ten studies were included in the qualitative synthesis. NOS scores ranged from 5 to 9 stars, with recurring limitations in the comparability domain. Four studies provided sufficient data for the meta-analysis of P300 latency. The combined estimate under a random-effects model demonstrated a statistically significant prolongation of latency in individuals with epilepsy compared to controls (SMD = 1.29; 95% CI: 1.03–1.54; $p < 0.001$), with no evidence of statistical heterogeneity ($I^2 = 0\%$; $\tau^2 = 0.00$; $Q(3) = 2.01$; $p = 0.57$). Publication bias tests did not indicate significant asymmetry (Begg $p = 0.333$; Egger $p = 0.303$), although the small number of studies limits statistical power. In the integrative synthesis of findings, prolonged latency was most frequently associated with poorer performance in global cognition, attention, processing speed, and executive functions. Reduced amplitude was associated with impairments in attention, executive functions, and working memory. Subgroups with greater clinical severity, including drug-resistant epilepsy and polytherapy, presented combined alterations of prolonged latency and reduced amplitude accompanied by worse cognitive performance. **Conclusion:** The evidence indicates that P300 is a sensitive electrophysiological marker of cognitive impairment in epilepsy, reflecting clinical characteristics of the disease and the effects of treatment, with potential complementary application to neuropsychological assessment.

Keywords: Epilepsy; P300; Cognitive Impairment; Systematic Review.

Sumário

Lista de abreviaturas e siglas

ADHD – Attention-deficit/hyperactivity disorder

AEDs – Antiepileptic drugs

EEG – Eletroencefalograma

ERP – Event-related potentials

FAEs – Fármacos antiepilépticos

ILAE – International league against epilepsy

NOS – Newcastle-ottawa scale

OMS – Organização mundial da saúde (*World Health Organization*)

P300 – Componente P300 dos potenciais evocados

PEEs – Potenciais evocados por eventos

PPGNC – Programa de Pós-Graduação em Neurociências e Comportamento

PRISMA – Preferred reporting items for systematic reviews and meta-analyses

REML – Restricted maximum likelihood

SMD – Standardized mean differences

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É amplamente reconhecido que a epilepsia é um distúrbio neurológico crônico e complexo, caracterizado por um conjunto heterogêneo de sinais e sintomas que abrangem diferentes etiologias, tipos de crises, graus de severidade e prognósticos. Esses aspectos estão associados a um padrão de excitabilidade neuronal anormal, responsável pela ocorrência de crises recorrentes (Fisher et al., 2005). No âmbito diagnóstico, a *International League Against Epilepsy* (ILAE) define epilepsia como uma doença do cérebro caracterizada por pelo menos um dos seguintes critérios: (a) ocorrência de duas crises não provocadas (ou reflexas) com intervalo superior a 24 horas; (b) ocorrência de uma crise não provocada (ou reflexa) acompanhada de probabilidade de novas crises semelhante ao risco geral de recorrência, de pelo menos 60%, observado após duas crises não provocadas, ao longo dos 10 anos seguintes; ou (c) diagnóstico de uma síndrome epiléptica (ILAE, 2014; Fisher et al., 2014).

Sob a perspectiva epidemiológica, a doença constitui um relevante problema de saúde pública devido à sua elevada prevalência global e às importantes repercussões neurobiológicas, psicológicas e sociais associadas. Estima-se que entre 0,5% e 1% da população mundial viva com a condição, o que corresponde a mais de 50 milhões de pessoas (World Health Organization, 2019). No Brasil, dados do Ministério da Saúde indicam prevalência aproximada de 1,8%, o que representa cerca de 4 milhões de indivíduos. A incidência anual é estimada em 100 casos por 100 mil habitantes, aproximadamente 150 mil novos diagnósticos por ano, sem contar com os casos que permanecem subnotificados (Ministério da Saúde, 2013).

A epilepsia frequentemente se inicia na infância ou adolescência, de modo que muitos pacientes convivem com a condição por um longo período e enfrentam impactos que vão além do controle das crises (Hermann et al., 2012). Alterações cognitivas são descritas como comuns e podem repercutir no desempenho escolar e ocupacional, contribuindo também para indicadores

socioeconômicos menos favoráveis (Vinter et al., 2022). Estudos com pacientes recém-diagnosticados, incluindo crianças e adultos, indicam que uma parcela expressiva já apresenta dificuldades cognitivas no início da epilepsia, após poucas crises e antes mesmo do início do tratamento com fármacos antiepilépticos (FAEs) (Vinter et al., 2022).

Historicamente, não obstante, a assistência em saúde concentrou-se sobretudo no controle das crises, e os sintomas cognitivos foram frequentemente atribuídos à atividade ictal, sustentando de forma implícita a ideia de que o controle das crises seria, por si só, uma "cura" para as dificuldades cognitivas. Essa visão tradicional, de caráter "*epilepsy-centric*" (centrada na epilepsia), tem sido progressivamente revisada por modelos etiológicos mais recentes, que consideram os problemas neuropsicológicos como comorbidades da epilepsia, podendo ser consequência da condição, mas também anteceder o seu início e/ou compartilhar uma base patológica subjacente. Assim, o controle das crises, embora essencial, não necessariamente resolve as dificuldades cognitivas, reforçando a necessidade de avaliação e manejo específicos dessas queixas (Hermann et al., 2012; Hermann et al., 2017; Helmstaedter & Witt, 2017; Vinter et al., 2022). Ainda nesse contexto, Vinter et al. (2022) destacam que as crises epilépticas representam apenas a "ponta do iceberg" dos desafios enfrentados por pessoas com epilepsia. Em determinados grupos, uma parcela expressiva desse quadro envolve dificuldades cognitivas, que podem ocorrer em até 80% dos casos (Vinter et al., 2022).

A epilepsia está associada a alterações em múltiplos domínios cognitivos, incluindo dificuldades de memória, aprendizagem, raciocínio, atenção, linguagem e funções executivas, como planejamento e controle inibitório, bem como elevada frequência de comorbidades psiquiátricas, especialmente depressão e ansiedade (World Health Organization, 2019; Šarić Jurić

et al., 2021; Wang et al., 2025). Na epilepsia do lobo temporal, prejuízos de aprendizagem espacial e memória tendem a se destacar (Wang et al., 2025).

De modo geral, o comprometimento cognitivo, relatado pelos próprios indivíduos com epilepsia como um dos aspectos mais desafiadores da doença, configura-se como uma das principais comorbidades, afetando aproximadamente 20% a 50% dessa população (Fisher et al., 2005; Tavakoli et al., 2011). Esses prejuízos, somados ao estigma social e ao isolamento vivenciado, ampliam o ônus da condição e comprometem a qualidade de vida e a autonomia funcional (World Health Organization, 2019; Šarić Jurić et al., 2021).

Crises recorrentes e frequentes são reconhecidas como fatores associados ao declínio e à deterioração gradual da função cognitiva, e a duração da epilepsia tem sido relacionada à maior gravidade do comprometimento (Wang et al., 2025). Do ponto de vista neurobiológico, tais alterações cognitivas apresentam origem multifatorial, envolvendo a própria atividade epiléptica, alterações estruturais e funcionais das redes neurais e os efeitos prolongados do uso de FAEs, cuja ação pode ser bidirecional, contribuindo tanto para o controle das crises quanto para o comprometimento neuropsicológico, a depender do perfil farmacológico e da complexidade do esquema terapêutico adotado. Trata-se de componentes que interagem de forma complexa ao longo da evolução clínica (Tavakoli et al., 2011). Nesse cenário, Wang et al. (2025) defendem a relevância do acompanhamento longitudinal do funcionamento cognitivo, uma vez que os FAEs podem influenciar a cognição, com maior sensibilidade descrita para domínios como atenção, velocidade de reação e funções executivas.

Nessa direção, a epilepsia passou a ser compreendida como uma condição de rede, envolvendo o cérebro em múltiplos níveis de organização espacial e temporal. Essa mudança conceitual desloca a compreensão de um foco restrito a uma área cortical específica para a noção

de uma rede epiléptica ampla, que integra diferentes regiões, lobos e hemisférios cerebrais. Tal organização em rede apresenta caráter dinâmico e em constante evolução, reforçando a necessidade de abordagens inovadoras para sua caracterização e manejo. Essa perspectiva transformou o entendimento da condição e tem influenciado de forma significativa tanto a pesquisa quanto a prática clínica (Bröhl et al., 2024).

O diagnóstico inicial da epilepsia é clínico e pode ser apoiado por exames complementares. Entre eles, o eletroencefalograma (EEG) se destaca como exame de referência, com papel fundamental na avaliação, classificação e monitoramento da atividade epileptiforme (Kanda et al., 2009; Papaliagkas et al., 2023). Além disso, o registro dos sinais elétricos cerebrais em pessoas com epilepsia é essencial para compreender, de forma aprofundada, como a desregulação neurobiológica se relaciona a alterações cognitivas, uma vez que o EEG permite identificar padrões anormais de atividade elétrica que podem refletir disfunções de rede (Athira et al., 2025).

Desse modo, os potenciais evocados por eventos (PEEs) surgem como uma medida eletrofisiológica complementar aos testes neuropsicológicos, oferecendo parâmetros objetivos da atividade cortical relacionada ao processamento cognitivo. Entre esses potenciais, destaca-se o componente P300, registrado por meio do EEG, que corresponde a pequenas variações de voltagem observadas no traçado eletroencefalográfico e associadas à resposta cerebral a estímulos específicos (Sowndhararajan et al., 2018; Šarić Jurić et al., 2021).

Sob esse panorama, o P300 tem se consolidado como um biomarcador relevante da função cognitiva, por refletir de forma objetiva processos atencionais e de atualização da informação. Trata-se de um marcador sensível e não invasivo, amplamente utilizado na investigação da eficiência dos processos de atenção e memória de trabalho, por estar associado ao processamento consciente da informação e à alocação de recursos cognitivos. Por essas características, o P300

tem se mostrado particularmente útil na detecção precoce de comprometimentos cognitivos e na compreensão da interface entre epilepsia e desempenho cognitivo, conforme demonstrado em diferentes populações clínicas (Mudabbir et al., 2020; Jeżowska-Jurczyk et al., 2023; Papaliagkas et al., 2023; Athira et al., 2025).

Em termos eletrofisiológicos, o P300 manifesta-se como uma deflexão positiva no sinal do EEG, registrada predominantemente nas regiões centro-parietais. Sua distribuição no couro cabeludo ocorre, sobretudo, nos eletrodos da linha média (Fz, Cz e Pz), apresentando amplitude que tende a aumentar das regiões frontais para as parietais, conforme descrito por Polich (2007) e corroborado por Sowndhararajan et al. (2018).

A amplitude (μV) é definida como a diferença entre a média da linha de base de voltagem antes do estímulo e o pico positivo máximo da forma de onda, variando entre 5 e 20 μV. A latência (ms) corresponde ao intervalo entre o início do estímulo-alvo e o ponto de máxima amplitude positiva dentro de uma janela temporal, geralmente entre 250 e 500 ms após o estímulo. Esse potencial apresenta dois subcomponentes, P3a e P3b, sendo este último o mais estudado (Sowndhararajan et al., 2018). Nessa conjuntura, a amplitude reflete o grau de alocação de recursos atencionais e o processamento da informação, enquanto o prolongamento da latência está associado ao pior desempenho cognitivo (Fabiani et al., 1990; Polich et al., 1990; Šarić Jurić et al., 2021). Alterações nesses parâmetros e em sua topografia têm sido associadas a diferentes distúrbios neurológicos (Fabiani et al., 1990; Mudabbir et al., 2020).

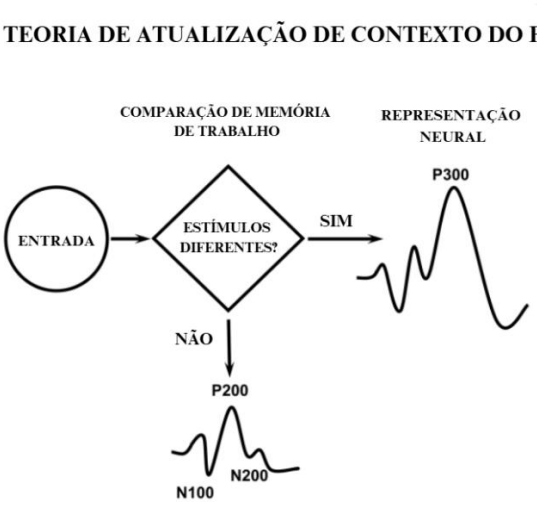
Diversos paradigmas experimentais têm sido empregados para a evocação do P300, sendo o *oddball* o mais utilizado. Nesse paradigma, estímulos frequentes são apresentados em sequência, intercalados com estímulos raros ou relevantes que exigem uma resposta diferenciada do

participante, desencadeando a deflexão positiva característica do P300 (Polich & Criado, 2006; Polich, 2007).

O modelo de atualização de contexto proposto por Polich (2007), esquematizado na Figura 1, sintetiza os processos cognitivos subjacentes à geração do P300, evidenciando a relação entre a detecção de estímulos relevantes, a alocação de recursos atencionais e a atualização da informação na memória de trabalho. De acordo com esse modelo teórico, o P300 é gerado quando um estímulo raro ou significativo exige a atualização do modelo neural do ambiente mantido na memória de trabalho. Nesse processo, o cérebro compara continuamente os estímulos recebidos com representações previamente estabelecidas; quando não há necessidade de atualização, observam-se apenas potenciais sensoriais iniciais, enquanto a identificação de um evento inesperado desencadeia a deflexão positiva característica do P300. Esse componente reflete, portanto, a alocação de recursos atencionais e a atualização da informação, estando diretamente relacionado aos parâmetros de amplitude e latência, amplamente utilizados como indicadores da eficiência do processamento cognitivo (Polich, 2007).

Figura 1

Ilustração esquemática do modelo de atualização de contexto do P300. Fonte: Polich, 2007.



Zhong et al. (2019), em uma revisão sistemática com meta-análise que incluiu vinte e sete estudos, observaram redução da amplitude e prolongamento da latência do P300 em indivíduos com epilepsia quando comparados a controles saudáveis. Os autores demonstram que o aumento da latência está associado a pior desempenho cognitivo, sendo esse padrão identificado em diferentes faixas etárias, incluindo crianças e adultos. Ademais, o prolongamento da latência foi descrito em distintos tipos de crises epilépticas, com heterogeneidade significativa tanto para os parâmetros de latência quanto de amplitude.

Esses achados convergem com evidências mais recentes, reforçando o P300 como um marcador sensível e objetivo associado à disfunção cognitiva em diferentes formas de epilepsia e útil para investigar a interface entre processos neurofisiológicos e desempenho neuropsicológico (Šarić Jurić et al., 2021; Mudabbir et al., 2020; Papaliagkas et al., 2023; Athira et al., 2025). Considerando a frequência com que alterações cognitivas são descritas nessa população e o impacto funcional a elas associado, torna-se relevante o reconhecimento precoce dessas dificuldades e o direcionamento de estratégias de acompanhamento e intervenção.

O presente estudo foi motivado pela necessidade de compreender, de forma integrada, as alterações neurofisiológicas e cognitivas associadas à epilepsia, especialmente diante da escassez de pesquisas voltadas à investigação do potencial evocado P300 como marcador eletrofisiológico associado a processos atencionais e de memória em populações brasileiras. Essa lacuna é ainda mais evidente no contexto amazônico, onde os estudos sobre epilepsia e cognição permanecem incipientes, apesar da elevada prevalência de doenças neurológicas na região.

Inicialmente, a pesquisa foi concebida como uma investigação empírica voltada à análise do P300 em indivíduos com epilepsia do lobo temporal residentes na região metropolitana de Belém do Pará. Entretanto, diante das limitações temporais e éticas associadas à coleta de dados clínicos

durante o período de execução do estudo, e em consonância com as normas do Programa de Pós-Graduação em Neurociências e Comportamento (PPGNC/UFPA), a pesquisa foi reestruturada no formato de dissertação com artigo científico. O estudo passou, então, a ser conduzido por meio de uma revisão sistemática da literatura, seguindo as recomendações do protocolo PRISMA, preservando o eixo teórico-metodológico originalmente proposto e o interesse central na relação entre parâmetros eletrofisiológicos do P300 e alterações cognitivas na epilepsia.

Objetivos

Objetivo geral

- Analisar a relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo em indivíduos com epilepsia, por meio de uma revisão sistemática da literatura.

Objetivos específicos

- Identificar os estudos que investigaram os parâmetros do P300 em indivíduos com diagnóstico de epilepsia;
- Avaliar a qualidade metodológica e o risco de viés dos estudos incluídos;
- Realizar uma meta-análise dos estudos que apresentaram dados comparáveis sobre a latência do P300, visando estimar a diferença média entre indivíduos com epilepsia e grupos controles;
- Verificar as correlações entre os parâmetros eletrofisiológicos do P300 e o desempenho cognitivo reportado;
- Discutir as implicações dos resultados para o uso do P300 como ferramenta eletrofisiológica complementar de disfunção cognitiva na epilepsia.

Esta pesquisa se justifica pela necessidade de uma síntese sistemática atualizada que integre as evidências disponíveis mais recentes sobre as alterações dos parâmetros do potencial evocado P300 em indivíduos com epilepsia e suas associações com o desempenho cognitivo.

O artigo intitulado "*The relationship between P300 event-related potential parameters and cognitive impairment in epilepsy: A systematic review and meta-analysis*" está estruturado no formato de artigo científico, obedecendo às normas de formatação e organização estabelecidas pela revista internacional *Epilepsy & Behavior* (Elsevier). O periódico é classificado como Qualis A3 na área de Medicina II, conforme a Plataforma Sucupira, e constitui um veículo de referência para a divulgação de pesquisas científicas voltadas à epilepsia, cognição e comportamento.

Artigo

The relationship between P300 evoked potential parameters and cognitive impairment in epilepsy: A systematic review and meta-analysis

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The relationship between P300 evoked potential parameters and cognitive impairment in epilepsy: A systematic review and meta-analysis

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Abstract: Epilepsy is a major public health condition affecting more than 50 million people worldwide and is frequently associated with cognitive impairment involving attention, memory, and executive functions. Event-related potentials, particularly the P300 component, have emerged as objective neurophysiological markers of cognitive processing. This study presents a systematic review and meta-analysis evaluating the relationship between P300 parameters and cognitive impairment in individuals with epilepsy. **Methodology:** A systematic review was conducted in the PubMed and LILACS databases using the descriptors "Epilepsy" AND "P300," in accordance with PRISMA guidelines. Studies published between January 2020 and June 2025 were included without language restrictions. Study selection was performed independently by two reviewers. Observational studies and clinical trials assessing P300 parameters alongside measures of cognitive performance in individuals with epilepsy were included. Methodological quality was evaluated using the Newcastle–Ottawa Scale (NOS). When sufficient quantitative data were available, a meta-analysis of P300 latency was conducted using standardized mean differences (SMD) under a random-effects model with Restricted Maximum Likelihood (REML) estimation. Due to heterogeneity in cognitive instruments and statistical reporting, associations between P300 parameters and cognitive domains were synthesized through a structured integrative synthesis. **Results:** Ten studies met the inclusion criteria. NOS scores ranged from 5 to 9 stars, with most studies showing limited control of confounders in the comparability domain. Four studies were included in the meta-analysis. The pooled effect size demonstrated significantly prolonged P300 latency in individuals with epilepsy compared with healthy controls (SMD = 1.29; 95% CI: 1.03–1.54; $p < 0.001$), with no evidence of heterogeneity ($I^2 = 0\%$; $\tau^2 = 0.00$; $Q(3) = 2.01$; $p = 0.57$). No influential outliers were identified, and publication bias tests were non-significant (Begg $p = 0.333$; Egger $p = 0.303$), although the small number of studies limits statistical power. The structured integrative synthesis revealed that prolonged P300 latency was consistently associated with poorer global cognition, attention, processing speed, and executive function, whereas reduced P300 amplitude was primarily associated with deficits in attention, executive function, and working memory. More severe clinical subgroups exhibited combined latency prolongation and amplitude reduction, accompanied by greater cognitive impairment. **Conclusion:** The P300 event-related potential constitutes a sensitive and clinically relevant neurophysiological marker of cognitive impairment in epilepsy. Alterations in latency and amplitude reflect disease severity and potential treatment-related effects. Integration of P300 assessment with neuropsychological evaluation may enhance clinical monitoring and therapeutic decision-making. Future studies should prioritize standardized P300 protocols and longitudinal designs to further validate its role as a neurophysiological marker in epilepsy.

Keywords: Epilepsy; Cognitive Impairment; Event-Related Potentials; P300; Antiepileptic Drugs; Cannabidiol; Systematic Review; Meta-analysis.

1. Introduction

Epilepsy is a chronic neurological disorder characterized by a persistent predisposition to spontaneous epileptic seizures, accompanied by neurobiological, cognitive, psychological, and social consequences [1]. It represents a major public health problem due to its high global prevalence, affecting approximately 0.5% to 1% of the population worldwide, corresponding to more than 50 million individuals [2].

Beyond seizures, epilepsy is frequently associated with significant functional impairments, including deficits in memory, learning, attention, language, and executive functions, as well as a high prevalence of psychiatric comorbidities such as depression and anxiety [2,3]. Cognitive dysfunction is recognized as one of the most challenging comorbidities affecting individuals with epilepsy and is reported in approximately 20% to 50% of patients [4]. These impairments, combined with social stigma and reduced autonomy, substantially increase disease burden and negatively impact quality of life [2,3].

The etiology of cognitive comorbidities in epilepsy is complex and multifactorial. Cognitive alterations may be present at diagnosis and often persist or worsen throughout the clinical course, depending on factors such as epilepsy type, localization of epileptiform activity, disease duration, seizure frequency, and the bidirectional effects of antiepileptic drugs (AEDs), which may contribute both to seizure control and cognitive dysfunction depending on their pharmacological profile and treatment complexity [5].

The diagnosis of epilepsy is primarily clinical and may be supported by complementary examinations. Among these, electroencephalography (EEG) remains the reference method for evaluation, classification, and monitoring of epileptiform activity [6,7]. In addition, the recording of cerebral electrical activity provides important insights into the relationship between

neurobiological dysregulation and cognitive alterations, as EEG allows the identification of abnormal electrical patterns that may reflect large-scale network dysfunctions [8].

Among the tools used to assess cognitive performance in individuals with epilepsy, event-related potentials (ERPs) have emerged as electrophysiological measures complementary to neuropsychological assessment, offering objective indices of cortical activity associated with cognitive processing. Within this framework, the P300 event-related potential stands out as a sensitive, objective, and non-invasive marker widely used to investigate attentional processes and working memory [6,9]. Recorded through EEG, the P300 corresponds to small voltage fluctuations time-locked to specific stimuli and reflects conscious information processing and the allocation of attentional resources.

From an electrophysiological perspective, the P300 is characterized by a positive deflection predominantly observed over centro-parietal scalp regions, with a scalp distribution mainly over midline electrodes. Alterations in P300 parameters, particularly latency prolongation and amplitude reduction, have been consistently associated with cognitive impairment and various neurological disorders [9–12].

Previous studies have demonstrated that individuals with epilepsy exhibit increased P300 latency and reduced amplitude compared with healthy populations, indicating delayed information processing and reduced efficiency of attentional and working memory mechanisms [6,9]. In addition, growing interest has focused on the influence of therapeutic regimens, particularly monotherapy and polytherapy with AEDs, on cognitive outcomes in epilepsy [10,13]. In this context, the P300 represents a valuable tool for investigating both disease-related and treatment-related cognitive effects.

Despite the existence of studies addressing cognitive impairment in epilepsy, recent systematic reviews specifically synthesizing the evidence on the use of the P300 as a neurophysiological measure associated with cognitive performance in epilepsy remain limited. This gap underscores the need for a rigorous synthesis of the available evidence.

Therefore, this study aims to systematically review the literature on the relationship between electrophysiological P300 parameters, particularly latency and amplitude, and cognitive performance in individuals with epilepsy.

2. Methodology

2.1. Study type

This study consisted of a systematic literature review conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [14], aiming to synthesize evidence on the relationship between electrophysiological P300 parameters and cognitive performance in individuals with epilepsy.

When quantitative data were sufficiently homogeneous, a meta-analysis was additionally performed. In cases where quantitative pooling was not feasible, a structured integrative synthesis was conducted.

2.2. Search strategy

A systematic search was performed in the electronic databases PubMed and LILACS, covering publications indexed between January 2020 and June 2025. The search strategy was based on the descriptors “Epilepsy” AND “P300”, combined using the Boolean operator AND. This strategy was selected to maximize sensitivity for identifying studies evaluating P300 in epileptic populations, given the relatively limited number of publications in this field. No language restrictions were applied, and studies published in any language were considered eligible.

Study selection was conducted independently by two reviewers through an initial screening of titles and abstracts, followed by full-text evaluation of potentially eligible articles. Disagreements regarding study inclusion or exclusion were resolved by consensus or, when necessary, by consultation with a third reviewer.

2.3. Selection criteria

Studies were included if they met all of the following criteria: (1) original peer-reviewed observational studies with cross-sectional or longitudinal designs, or clinical trials; (2) inclusion

of individuals diagnosed with epilepsy; (3) assessment of the P300 event-related potential using electroencephalography, with quantitative reporting of latency and/or amplitude; and (4) evaluation of cognitive performance using standardized neuropsychological tests or validated cognitive screening instruments. Studies were excluded if they were reviews, meta-analyses, theoretical papers, case reports, editorials, letters, or conference abstracts; if they did not include quantitative P300 or cognitive measures; or if insufficient methodological information was available to allow data extraction.

2.4. Methodological quality assessment

The methodological quality of the included studies were assessed using the Newcastle–Ottawa Scale (NOS) [15]. As most included studies had a cross-sectional design, an adapted version of the NOS for cross-sectional studies was applied, as commonly adopted in systematic reviews, despite the absence of formal validation. Risk of bias was evaluated across three domains: selection, comparability, and outcome/exposure. Studies scoring 7–9 stars were classified as low risk of bias, 5–6 stars as moderate risk, and ≤4 stars as high risk.

2.5. Data extraction

Data extracted from the included studies comprised sociodemographic characteristics (age, sex, sample size), clinical features (type of epilepsy, disease duration, seizure frequency), electrophysiological parameters (P300 latency and amplitude), cognitive domains assessed, and therapeutic regimens when reported. Therapeutic variables were considered descriptively, as contextual factors, and were not treated as primary analytical outcomes.

2.6. Meta-analysis of P300 latency

Due to heterogeneity in study designs and cognitive assessment methods, a primarily qualitative synthesis was performed. When sufficient quantitative data were available, a meta-

analysis focusing on P300 latency was conducted, as this parameter was the most consistently reported across studies. Only studies that provided sample size, mean latency, and standard deviation for both epilepsy and control groups were included in the quantitative synthesis. Studies lacking a control group were excluded from the meta-analysis and were instead addressed descriptively in the qualitative synthesis.

Effect sizes were calculated as standardized mean differences (SMD), given the variability in latency measurement scales across studies. A random-effects model using the Restricted Maximum Likelihood (REML) estimator was applied to account for expected clinical and methodological heterogeneity. Heterogeneity was assessed using Cochran's Q test, the I^2 statistic, and τ^2. Forest plots were generated to present individual and pooled estimates with 95% confidence intervals, and funnel plots were used to visually assess potential small-study effects. Begg's rank correlation and Egger's regression tests were applied to statistically evaluate funnel plot asymmetry. All statistical analyses were conducted using Jamovi software (version 2.7.6).

2.7 *Integrative analysis*

Given the heterogeneity of cognitive assessment instruments and the variability in statistical reporting across the included studies, a quantitative synthesis of associations between P300 parameters and cognitive performance was not feasible. Therefore, an integrative analysis was conducted to systematically organize and compare the reported patterns of association between P300 latency and amplitude and specific cognitive domains.

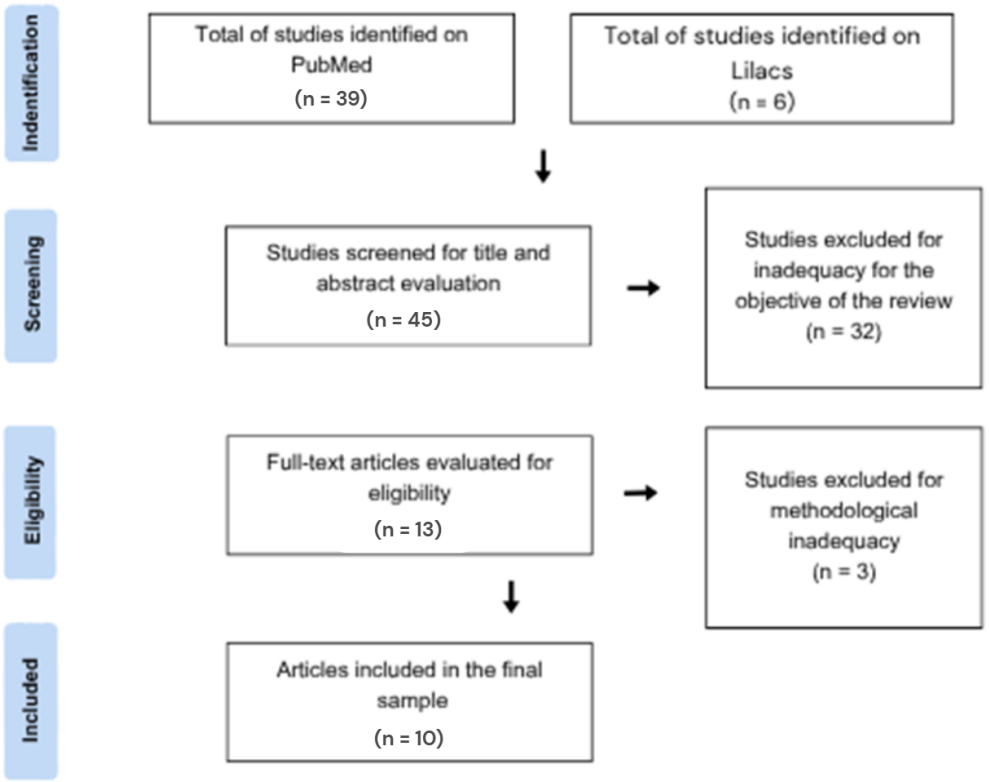
Studies were grouped according to the type of evidence presented, including: (i) direct statistical correlations; (ii) group-based comparisons between epilepsy subtypes or treatment regimens; and (iii) combined alterations in latency and amplitude associated with clinical severity.

3. Results

A total of 45 publications were identified in the PubMed (n = 39) and LILACS (n = 6) databases. After screening titles and abstracts, 32 studies were excluded for not meeting the eligibility criteria, leaving 13 articles for full-text evaluation. Of these, three were excluded for not evaluating cognitive performance in relation to P300 parameters. Thus, ten studies met the inclusion criteria and were incorporated into the qualitative synthesis (Figure 1).

Figure 1

Summary flowchart of the search strategy for studies included in this systematic review on the relationship between P300 and epilepsy, according to the PRISMA guidelines.



Source: Study data, 2025.

The main methodological characteristics and principal findings of the selected studies are summarized in Table 1, including the authors, year of publication, country of origin, objectives, design, main results and conclusions of the analyzed studies.

Table 1

Summary of the 10 included studies, presenting Author/year of publication, country of study, objective, methodology, results and conclusions.

Author/ Year	Country	Objective	Methodology	Main Results	Conclusions
Mudabbir et al. (2020)	India	Evaluate P300 recorded by MEG; assess its relationship with cognitive dysfunction in MTLE.	Prospective case–control study using MEG-based oddball paradigms and cognitive assessment.	Reduced visual P300 amplitude in TLE-HS, more pronounced in right HS. No auditory P300 differences. Correlated with visuospatial attention and working memory..	Reduced visual P300 amplitude is associated with cognitive impairment in TLE-HS and may serve as a complementary assessment tool.
Fang et al. (2021)	China	Assess cognitive impairment in children with BECTS and ADHD.	Prospective study using P300, WISC, and continuous performance tests in patients and controls.	Prolonged P300 latency was observed alongside cognitive impairment.	Polytherapy worsened cognitive outcomes; P300 is a useful tool for monitoring cognitive dysfunction in epilepsy.
Šarić Jurić et al. (2021)	Croatia	Evaluate the cognitive impact of antiepileptic drug monotherapy and polytherapy using P300.	Cross-sectional study using auditory P300 in epilepsy patients and controls.	Increased latency, reduced amplitude; worse cognition with polytherapy.	Polytherapy worsens cognition; P300 is useful for monitoring cognitive dysfunction in epilepsy.

Author/ Year	Country	Objective	Methodology	Main Results	Conclusions
Jeżowska-Jurczyk et al. (2023)	Poland	Cognitive effects of antiepileptic monotherapy vs. polytherapy assessed by P300.	Cognitive effects of antiepileptic monotherapy vs. polytherapy assessed by P300.	Polytherapy and carbamazepine were linked to prolonged P300 latency and poorer cognition; lamotrigine showed a more favorable profile.	Polytherapy worsens cognition; P300 is useful for monitoring cognitive dysfunction in epilepsy.
Papaliagkas et al. (2023)	Greece	Assess cognitive dysfunction in MRI-negative epilepsy.	Assess cognitive dysfunction in MRI-negative epilepsy.	Prolonged P300 latency associated with poorer performance in attention and processing speed.	Subtle cognitive deficits are present in MRI-negative epilepsy and can be detected using P300.
Gangemi et al. (2023)	Italy	Evaluate neurophysiological (P300) and cognitive parameters in temporal lobe epilepsy.	Case-control study using P300, MoCA, and MMSE.	Increased P300 latency, reduced amplitude, and cognitive deficits.	P300 sensitively reflects cognitive impairment in TLE.

Author/ Year	Country	Objective	Methodology	Main Results	Conclusions
Hasan et al. (2023)	Egypt	Evaluate cognitive dysfunction in epilepsy using the P300.	Case–control study including patients with epilepsy and healthy controls. Cognitive assessment was performed with MoCA, and auditory P300 was recorded using the oddball paradigm.	Patients with epilepsy showed prolonged P300 latency and reduced amplitude compared to controls. Polytherapy and abnormal EEG findings were associated with worse P300 parameters.	The P300 is a sensitive marker of cognitive impairment in epilepsy, influenced by disease characteristics and antiepileptic treatment.
Glatt et al. (2024)	Israel	Evaluate the effects of cannabidiol-enriched oil in drug-resistant epilepsy	Prospective study with cognitive assessment and P300.	Responders showed seizure reduction and cognitive improvement, while non-responders exhibited reduced P300 amplitude.	Cannabidiol treatment produced heterogeneous cognitive and electrophysiological effects; P300 may assist in monitoring therapeutic response.

Author/ Year	Country	Objective	Methodology	Main Results	Conclusions
Shafiyev & Karadaş (2024)	Türkiye	To evaluate the cognitive effects of AEDs using MoCA and P300/N200.	Prospective study with patients with epilepsy and controls; comparison between monotherapy and polytherapy.	Polytherapy was associated with worse cognitive performance and altered P300/N200 parameters, particularly with topiramate and carbamazepine.	Polytherapy with AEDs is linked to greater cognitive impairment.
Athira et al. (2025)	India	To assess cognition in refractory (DRE) and newly diagnosed (NDE) epilepsy using P300 and neuropsychological tests.	Cross-sectional study. 88 DRE patients, 88 NDE patients, and 88 controls. Evaluation with P300, MoCA , FAB, and Digit Span .	DRE and NDE presented longer P300 latency and lower amplitude. The DRE group had worse cognitive performance. The number of seizures correlated negatively with performance.	Inadequate seizure control and polytherapy are associated with greater cognitive impairment. The P300 demonstrated high sensitivity to these changes.

Source: Study data, 2025

Although several studies reported cognitive performance alongside electrophysiological findings, it is important to note that direct statistical associations between P300 parameters and cognitive measures were not uniformly assessed across all included studies. Therefore, results related to cognitive outcomes and clinical variables are presented descriptively when applicable.

3.1. *Methodological quality* and the risk of bias *assessment*

Methodological quality was assessed using the Newcastle–Ottawa Scale (NOS), a star-based instrument developed for the evaluation of non-randomized studies in meta-analyses. The NOS examines three methodological domains: Selection, Comparability, and Exposure or Outcome, depending on study design. The Selection domain includes four items, the Comparability domain allows a maximum of two stars, and the Exposure/Outcome domain includes three items, resulting in a maximum total score of nine stars. Higher scores reflect better methodological quality. The results of the quality assessment are presented in Table 2.

Table 2.

Methodological Quality Assessment of the Included Studies Using the Newcastle–Ottawa Scale (NOS)

Studies	Items								
	Selection				Comparability	Exposure/ Outcome			Score
	1	2	3	4	2	1	2	3	
Mudabbir et al. (2020)	★	★	★	★	★	★	★	-	7/9
Fang et al. (2021)	★	★	-	★	★	★	★	-	6/9
Šarić Jurić et al. (2021)	★	★	★	★	★	★	★	-	7/9
Jeżowska-Jurczyk et al. (2023)	★	★	-	★	★	★	★	-	6/9
Papaliagkas et al. (2023)	★	★	-	★	★	★	★	-	6/9
Gangemi et al. (2023)	★	-	-	★	★	★	★	-	5/9

Studies	Items								
	Selection				Comparability	Exposure/ Outcome			Score
	1	2	3	4	2	1	2	3	
Hasan et al. (2023)	★	★	★	★	★★	★	★	★	9/9
Glatt et al. (2024)	★	-	-	★	★	★	★	-	5/9
Shafiyev et al. (2024)	★	★	-	★	★	★	★	-	6/9
Athira et al. (2025)	★	★	★	-	★	★	★	-	6/9

Source: Study data, 2025.

Among the case-control studies, three obtained seven or more stars (Mudabbir et al., 2020 [11]; Šarić Jurić et al., 2021 [5]; Hasan et al., 2023 [21]), indicating higher methodological scores according to the NOS. Two case-control studies obtained six stars (Jeżowska-Jurczyk et al., 2023 [7]; Athira et al., 2025 [10]), while one study received five stars (Gangemi et al., 2023 [9]).

Among the cross-sectional studies, three obtained six stars (Fang et al., 2021 [12]; Papaliagkas et al., 2023 [8]; Shafiyev & Karadaş, 2024 [6]), and one study obtained five stars (Glatt et al., 2024 [13]).

Overall, nine of the ten included studies received only one star in the comparability domain, reflecting limited adjustment for potential confounding variables. In most cases, comparability was restricted to age adjustment, without consistent control for other relevant factors such as education level, epilepsy subtype, seizure frequency, or antiepileptic medication use. Hasan et al. (2023) [21] achieved the maximum score in the comparability domain, indicating more comprehensive control of confounders.

In the exposure/outcome domain (depending on study design), lower scores were mainly related to incomplete reporting regarding sample representativeness, follow-up adequacy, or justification for exclusions. For cross-sectional studies assessed using the adapted version of the Newcastle–Ottawa Scale, the item originally related to longitudinal follow-up was interpreted in terms of clarity of P300 acquisition procedures and consistency of electrophysiological protocols across groups. These methodological considerations should be considered when interpreting the findings of this review.

3.2 Meta-analysis of P300 latency

Because P300 latency was the most consistently reported electrophysiological parameter across the included studies, a quantitative synthesis was conducted to estimate the overall difference in P300 latency between individuals with epilepsy and healthy control groups. A meta-analysis was performed including studies that reported sufficient quantitative data (sample size, mean latency, and standard deviation) for both groups.

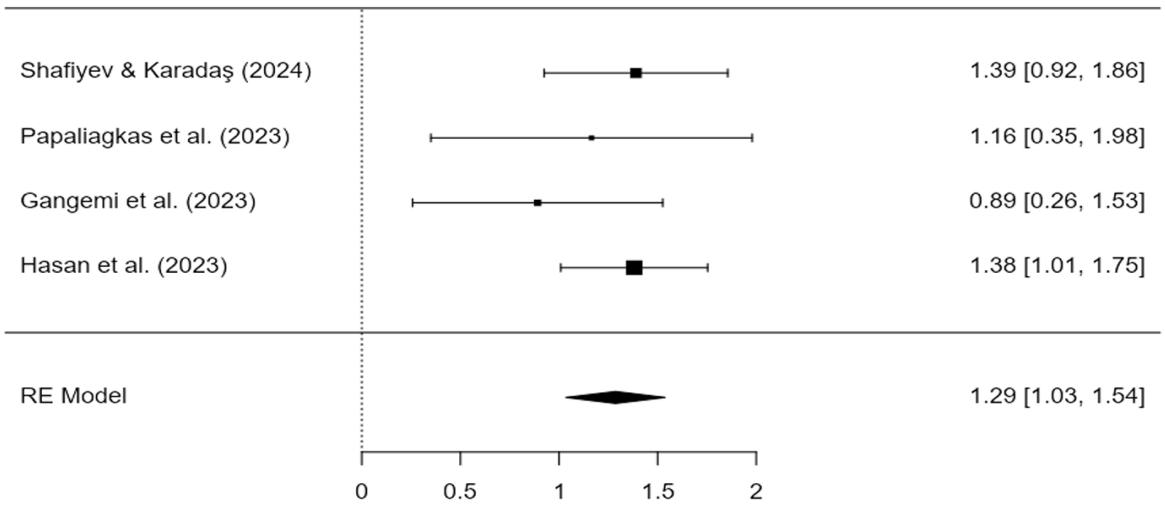
Four studies were included in the meta-analysis. A random-effects model using the Restricted Maximum-Likelihood (REML) estimator revealed a statistically significant pooled effect size (SMD = 1.29; 95% CI: 1.03–1.54; $z = 10.03$; $p < 0.001$), indicating longer P300 latency in individuals with epilepsy compared to healthy controls.

No statistical evidence of heterogeneity was observed across studies ($I^2 = 0\%$; $\tau^2 = 0.00$). Cochran's Q test was not statistically significant ($Q(3) = 2.01$; $p = 0.57$). Examination of studentized residuals and Cook's distances did not identify outliers or excessively influential studies. Publication bias tests (Begg's rank correlation and Egger's regression) did not indicate significant funnel plot asymmetry ($p = 0.33$ and $p = 0.30$, respectively), although the small number of included studies ($k = 4$) limits the statistical power of these analyses.

The forest plot shown in Figure 2 presents the pooled standardized mean differences (SMD) between individuals with epilepsy and healthy control groups, with effect sizes weighted according to inverse variance under the random-effects model. Heterogeneity statistics (Q, I^2, and τ^2) are provided to facilitate interpretation of the pooled estimates.

Figure 2

Forest plot of the meta-analysis comparing P300 latency between individuals with epilepsy and healthy control groups. The pooled estimate was calculated using a random-effects model and expressed as standardized mean differences (SMD). Positive values indicate longer P300 latency in the epilepsy groups.



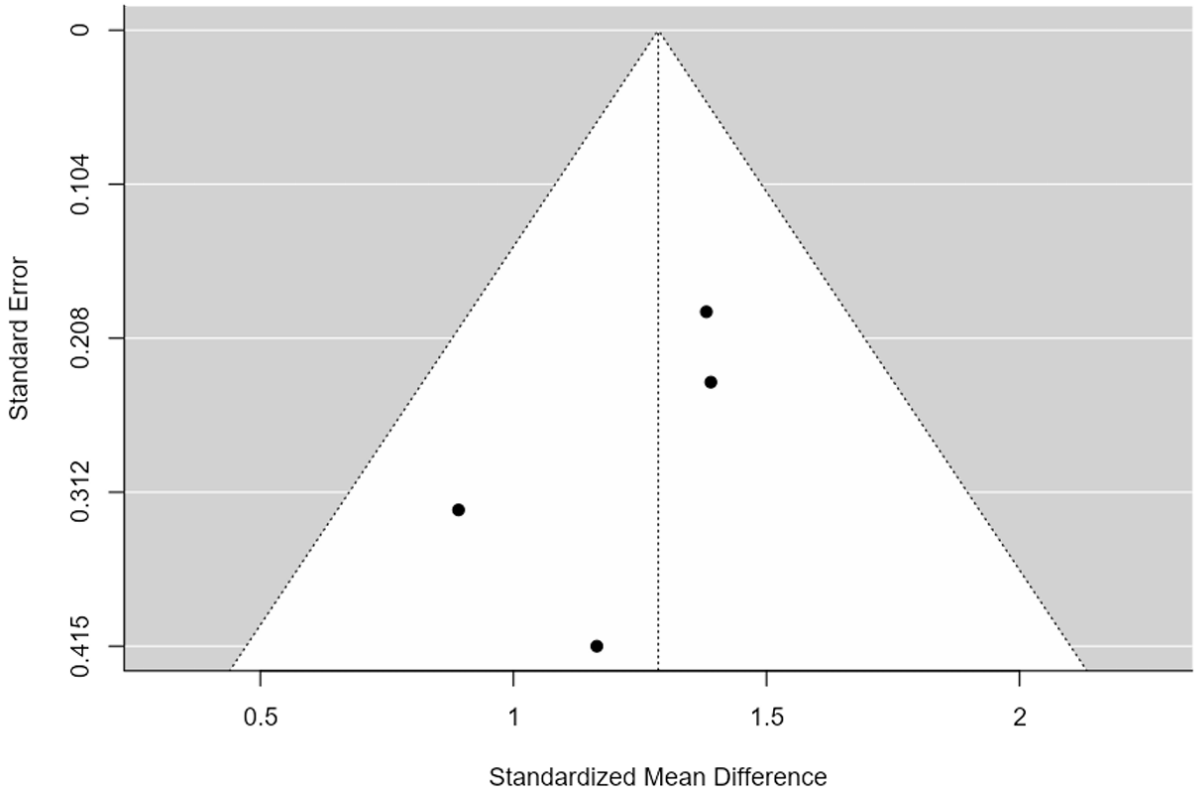
Source: Study data, 2025.

3.3 *Publication Bias Assessment*

Publication bias was assessed through visual inspection of the funnel plot and formal statistical tests. The distribution of standardized mean differences appeared reasonably symmetrical around the pooled estimate, with no evident indication of small-study effects. This visual inspection was supported by non-significant results from Begg's rank correlation test ($p = 0.333$) and Egger's regression test ($p = 0.303$), indicating no statistical evidence of funnel plot asymmetry.

Figure 3

Funnel plot for assessment of publication bias in the meta-analysis of P300 latency.



Source: Study data, 2025.

The meta-analysis conducted for P300 latency demonstrated a significant pooled effect, indicating prolonged latency in individuals with epilepsy compared to healthy controls. However, a quantitative synthesis of the association between P300 parameters and cognitive performance was not feasible, due to heterogeneity in the cognitive assessment instruments employed (MoCA, MMSE, EpiTrack, and specific neuropsychological batteries), as well as the absence of comparable correlation coefficients across studies.

3.4 *Integrative analysis of P300 parameters and cognitive domains*

Given this methodological limitation, an integrative analysis was performed to systematically describe the reported associations between P300 parameters (latency and amplitude) and cognitive domains across the included studies.

3.4.1 *P300 latency and cognitive domains*

Prolonged P300 latency was primarily reported in association with poorer performance in global cognition and attentional/executive domains, with additional reports involving processing speed and memory. Gangemi et al. (2023) reported a negative correlation between P300 latency and MoCA and MMSE scores, indicating that longer latencies were associated with poorer global cognitive performance in patients with temporal lobe epilepsy. Papaliagkas et al. (2023), in a cohort with MRI-negative epilepsy, described prolonged P300 latency accompanied by inferior performance in tasks related to attention, processing speed, and verbal memory. Jeżowska-Jurczyk et al. (2023) observed an association between increased latency and reduced performance in tasks involving executive control and attention. Hasan et al. (2023) reported longer latency associated with lower MoCA scores, as well as with higher seizure frequency. Collectively, these findings suggest a recurrent association between prolonged P300 latency and impairment in global cognition and attentional/executive domains.

3.4.2 *P300 amplitude and cognitive domains*

Reduced P300 amplitude was primarily reported in association with impairments in attentional domains, executive function, working memory, and global cognition. Gangemi et al. (2023) observed that lower amplitudes were associated with poorer MoCA and MMSE scores. Jeżowska-Jurczyk et al. (2023) described an association between reduced amplitude and inferior performance in executive tasks. Šarić Jurić et al. (2021) reported lower amplitudes in patients

receiving polytherapy, accompanied by poorer global cognitive performance. Glatt et al. (2024) observed differences in P300 amplitude between treatment responders and non-responders, with distinct cognitive performance between groups. Athira et al. (2025) reported reduced amplitude in patients with drug-resistant epilepsy, accompanied by lower cognitive scores. Overall, reduced P300 amplitude was consistently associated with deficits in executive functioning, attention, and global cognitive performance.

3.4.3 *Combined alterations of latency and amplitude*

Gangemi et al. (2023), Hasan et al. (2023), and Athira et al. (2025) reported the simultaneous presence of prolonged latency and reduced amplitude in subgroups with greater clinical severity, including higher seizure frequency or greater treatment burden. These subgroups exhibited inferior performance in global cognition measures and executive domains. The coexistence of prolonged latency and reduced amplitude was predominantly observed in patients with drug-resistant epilepsy or under polytherapy, suggesting a cumulative electrophysiological expression of increased clinical burden.

Table 3 presents the distribution of reported associations between P300 parameters and specific cognitive domains across the included studies. The matrix structure allows identification of which domains were explicitly evaluated and described in association with prolonged P300 latency or reduced amplitude. Across studies, prolonged P300 latency was most frequently associated with global cognition and attentional/executive domains, whereas reduced amplitude was predominantly linked to executive dysfunction and global cognitive impairment. Associations with processing speed and memory were reported less consistently. Variations across studies reflect differences in cognitive instruments and domain-specific assessments employed.

Table 3

Associations between P300 parameters and cognitive domains in the included studies

Study	Latency ↑	Amplitude ↓	Global Cognition	Attention	Processing Speed	Executive Function	Memory
Gangemi et al., 2023	✓	✓	✓	—	—	—	—
Hasan et al., 2023	✓	✓	✓	—	—	—	—
Papaliagkas et al., 2023	✓	—	—	✓	✓	—	✓
Jeżowska-Jurczyk et al., 2023	✓	✓	—	✓	—	✓	—
Šarić Jurić et al., 2021	✓	✓	—	—	—	—	—
Glatt et al., 2024	—	✓	—	—	—	—	—
Athira et al., 2025	✓	✓	✓	—	—	✓	✓
Shafiyev & Karadaş, 2024	✓	✓	✓	—	—	—	—
Fang et al., 2021	✓	✓	✓	—	—	—	—
Mudabbir et al., 2020	—	✓	—	✓	—	✓	✓

Note. ✓ = The study reported an explicit association between the P300 parameter and the respective cognitive domain. Dash (—) indicates that the domain was either not evaluated or no explicit association with P300 parameters was described. Latency ↑ = Prolonged P300 latency; Amplitude ↓ = Reduced P300 amplitude.

4. Discussion

Overall, the ten included studies provided consistent evidence of cognitive alterations in individuals with epilepsy, with the P300 event-related potential emerging as a robust and sensitive neurophysiological assessment tool. Across different study designs, age groups, and epilepsy subtypes, individuals with epilepsy consistently exhibited alterations in P300 parameters, most commonly increased latency and reduced amplitude, which were frequently reported alongside deficits in memory, attention, executive functions, and cognitive processing speed. This pattern was further supported by the quantitative synthesis, in which the meta-analysis demonstrated a statistically significant prolongation of P300 latency in individuals with epilepsy compared with healthy controls.

From a neurophysiological perspective, P300 latency is widely interpreted as an index of stimulus evaluation and classification speed, reflecting the time required to detect and process task-relevant information, whereas P300 amplitude is related to the allocation of attentional resources and the degree of cognitive engagement during stimulus processing [9,20]. Longer P300 latencies have been consistently associated with slower cognitive processing and poorer performance across multiple cognitive domains, while reduced amplitudes have been linked to diminished attentional and working memory resources. Within this framework, the pattern of prolonged latency and reduced amplitude observed in individuals with epilepsy is consistent with disruptions in attentional and memory-related networks, providing a plausible neurophysiological basis for the cognitive alterations reported in the included studies [9,20].

In pediatric populations, Fang et al. [18] evaluated children with benign rolandic epilepsy, attention-deficit/hyperactivity disorder (ADHD), and their comorbidity using auditory P300 and

neuropsychological measures. Children with epilepsy associated with ADHD showed more pronounced P300 alterations, including longer latency and reduced amplitude, compared with those with epilepsy alone, ADHD alone, or healthy controls. These electrophysiological findings were accompanied by impairments in selective attention and working memory, highlighting the additive cognitive burden of epilepsy and neuropsychiatric comorbidities during neurodevelopment.

In adult populations, pharmacological factors were frequently identified as relevant contributors to cognitive outcomes. Šarić Jurić et al. [5] demonstrated prolonged P300 latency and reduced N200–P300 amplitudes in individuals with epilepsy compared with controls, with significantly greater impairment among patients receiving polytherapy. Carbamazepine was associated with worse cognitive and electrophysiological performance, whereas lamotrigine showed a more favorable profile. These findings were reinforced by Shafiyev and Karadaş [10], who reported that treatment regimens including topiramate or carbamazepine were associated with longer P300 latencies and lower cognitive scores, while lamotrigine- or levetiracetam-based therapies were associated with relatively preserved cognitive performance. Complementarily, Hasan et al. [21] demonstrated consistent P300 latency prolongation in adults with epilepsy while adequately controlling for multiple confounding variables, strengthening the association between electrophysiological slowing and cognitive dysfunction.

Disease severity and chronicity also emerged as important contextual factors. Athira et al. [8] compared individuals with drug-resistant epilepsy, newly diagnosed epilepsy, and healthy controls, showing that drug-resistant epilepsy was associated with significantly prolonged P300 latency, reduced amplitude, and poorer performance on MoCA, FAB, and digit span tests. These

findings underscore the cumulative impact of longer disease duration, higher seizure frequency, and exposure to multiple antiseizure medications on cognitive outcomes.

Epilepsy type and localization were likewise relevant. Gangemi et al. [17] reported increased P300 latency, reduced amplitude, and deficits in memory and verbal fluency in patients with temporal lobe epilepsy. Similarly, Mudabbir et al. [12], using magnetoencephalography, demonstrated lateralized reductions in P300 amplitude in individuals with unilateral hippocampal sclerosis, particularly in the right hemisphere, with significant correlations between electrophysiological abnormalities and executive dysfunction. Together, these findings support the P300 as a functional marker reflecting localized cortical and network-level dysfunction in focal epilepsies.

Cognitive alterations were also identified in epilepsy without evident structural abnormalities. Papaliagkas et al. [13] observed subtle cognitive deficits in MRI-negative epilepsy, with prolonged P300 latency associated with poorer performance on the EpiTrack test. Likewise, Jeżowska-Jurczyk et al. [16] found that a substantial proportion of patients with epilepsy of unknown etiology exhibited impairments in verbal memory and executive functions in association with increased P300 latencies. Notably, transient cognitive dysfunction related to interictal epileptiform discharges was described in some cases [13], suggesting that the P300 may capture dynamic and subclinical network disruptions not consistently detected by conventional neuropsychological assessment.

In the therapeutic context, Glatt et al. [19] evaluated adults with drug-resistant epilepsy treated with cannabidiol-enriched oil and reported heterogeneous cognitive and electrophysiological responses. Patients who responded clinically exhibited seizure reduction accompanied by improvements in cognitive performance, whereas non-responders showed

increased seizure frequency and a significant reduction in P300 amplitude. These findings support the potential utility of the P300 for monitoring individualized treatment response.

Taken together, the findings of this review indicate that the P300 is a sensitive electrophysiological marker of cognitive dysfunction in epilepsy, reflecting both disease-related characteristics—such as epilepsy type, localization, duration, and seizure burden—and treatment-related factors, including drug selection and polytherapy. Although increased latency and reduced amplitude were consistently observed, the magnitude and pattern of cognitive impairment varied across populations and methodological designs, underscoring the influence of specific clinical and contextual factors.

Heterogeneity among studies was anticipated due to variations in epilepsy subtypes, participant age, treatment regimens, and P300 acquisition protocols. A random-effects model was therefore applied to account for between-study variability. Although heterogeneity may reduce estimate precision, the consistent direction of P300 latency prolongation across studies supports the robustness of the findings.

Nevertheless, important limitations must be acknowledged. Methodological variability, including differences in elicitation paradigms, clinical characteristics, disease duration, and cognitive assessment tools, limited direct comparability and confined quantitative synthesis primarily to latency outcomes. In addition, the predominance of cross-sectional designs and small sample sizes restricts inferences regarding causality and longitudinal cognitive trajectories. Accordingly, the overall certainty of the evidence should be interpreted as low to moderate.

In conclusion, the available evidence supports the P300 as a clinically relevant and sensitive neurophysiological indicator of cognitive dysfunction in epilepsy. Integration of P300 measures with standardized neuropsychological assessment may enhance the objective

characterization of cognitive impairment and support personalized therapeutic monitoring. Future research should prioritize longitudinal designs, standardized P300 protocols, and multimodal approaches combining electrophysiology, neuropsychology, and neuroimaging to further elucidate the mechanisms underlying cognitive impairment in epilepsy.

5. Conclusion

The P300 event-related potential is a sensitive and clinically relevant functional marker for detecting cognitive changes in people with epilepsy, reflecting impairments in attention, working memory, and processing speed. This conclusion is supported by the quantitative synthesis, which demonstrated a consistent and statistically significant prolongation of P300 latency in individuals with epilepsy compared with healthy controls. In the pharmacological context, polytherapy particularly regimens including topiramate and carbamazepine, was associated with longer latencies and reduced amplitudes, whereas lamotrigine and levetiracetam were associated with relatively preserved electrophysiological and cognitive parameters. Individuals with drug-resistant epilepsy exhibited more pronounced P300 alterations and poorer neuropsychological performance, underscoring the relationship between seizure burden, treatment complexity, and cognitive outcome.

In temporal lobe epilepsy, marked cognitive deficits were consistently accompanied by prolonged P300 latency and reduced amplitude, suggesting slowed information processing and reduced attentional efficiency. Notably, P300 alterations were also observed in cryptogenic or MRI-negative epilepsy, indicating functional network dysfunction, particularly affecting executive domains. In pediatric epilepsies, such as benign rolandic epilepsy, the presence of neuropsychiatric comorbidities, including ADHD, was associated with more pronounced P300 abnormalities, especially in measures related to selective attention, inhibitory control, and processing speed. With

regard to emerging therapeutic approaches, prospective evidence involving cannabidiol suggested cognitive and clinical improvement in responders, accompanied by changes in P300 parameters, supporting its potential utility in monitoring treatment response.

Given the methodological heterogeneity of the included studies and the predominance of cross-sectional designs with moderate risk of bias, these findings should be interpreted with caution. Future research should prioritize longitudinal study designs, standardization of P300 acquisition protocols (including paradigm, modality, electrode placement, and measurement criteria), direct comparisons between monotherapy and polytherapy regimens, and multimodal integration of neuropsychological assessment, electrophysiology, and neuroimaging. Such approaches are essential to establish clinically meaningful thresholds and to further consolidate the role of the P300 as a complementary tool in the cognitive assessment and management of people with epilepsy.

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Considerações finais

Em suma, a presente dissertação teve como objetivo analisar, por meio de uma revisão sistemática da literatura, a relação entre os parâmetros do potencial evocado P300 e o comprometimento cognitivo em indivíduos com epilepsia. Apesar da heterogeneidade metodológica entre os estudos incluídos, a análise crítica das evidências disponíveis permitiu verificar que os objetivos propostos foram alcançados, possibilitando a integração estruturada dos achados eletrofisiológicos aos desfechos cognitivos e clínicos reportados, com a identificação de padrões convergentes.

De modo geral, os resultados indicam alterações nos parâmetros do P300, caracterizadas principalmente pelo prolongamento da latência e, em menor grau, pela redução da amplitude, em indivíduos com epilepsia quando comparados a grupos controle. Esses achados estão associados a prejuízos em domínios como atenção, velocidade de processamento da informação, memória de trabalho e funções executivas, sugerindo que o comprometimento cognitivo na epilepsia não se restringe à ocorrência das crises.

A análise dos estudos evidenciou ainda que tais alterações não se manifestam de maneira homogênea, variando de acordo com fatores clínicos e contextuais, como o tipo e a localização da epilepsia, a duração da doença, a frequência das crises e o perfil terapêutico adotado. Em particular, regimes de politerapia e determinadas classes de fármacos antiepilépticos mostraram-se associados a maior comprometimento cognitivo e a alterações mais pronunciadas nos parâmetros do P300, enquanto outros medicamentos apresentaram perfis cognitivos relativamente mais favoráveis.

Do ponto de vista metodológico, a revisão revelou heterogeneidade considerável entre os estudos incluídos, envolvendo diferenças nos paradigmas de elicitação do P300, nos instrumentos de avaliação cognitiva e no controle de variáveis de confusão.

Ainda assim, os achados desta dissertação sustentam o P300 como ferramenta eletrofisiológica sensível e objetiva, capaz de refletir alterações cognitivas associadas à epilepsia, especialmente quando utilizada de forma complementar à avaliação neuropsicológica. Nesse sentido, o P300 pode ser interpretado como marcador eletrofisiológico associado ao desempenho cognitivo, útil para investigação, monitoramento e aprofundamento da compreensão dos mecanismos neurofisiológicos subjacentes.

Por fim, destaca-se a necessidade de futuros estudos com amostras maiores, delineamentos longitudinais, padronização dos protocolos de registro do P300 e melhor controle de variáveis de confusão, além da ampliação de investigações em contextos ainda pouco explorados, como o brasileiro e o amazônico. A integração de dados eletrofisiológicos, neuropsicológicos e clínicos poderá contribuir de forma decisiva para o avanço do conhecimento sobre o comprometimento cognitivo na epilepsia e para o desenvolvimento de estratégias terapêuticas mais individualizadas.

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ANEXOS

ANEXO A - Newcastle–Ottawa Quality Assessment Scale – Case-Control Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ✸
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ✸
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ✸
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ✸
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ✸
   b) study controls for any additional factor ✸ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ✸
   b) structured interview where blind to case/control status ✸
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ✸
   b) no

3) Non-Response rate
   a) same rate for both groups ✸
   b) non respondents described
   c) rate different and no designation

ANEXO B - Newcastle–Ottawa Quality Assessment Scale – Adapted for Cross-Sectional Studies

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

(adapted for cross sectional studies)

Selection: (Maximum 5 scores)

1) Representativeness of the cases:

a) Truly representative of the HCC patients (consecutive or random sampling of cases). 1 score

b) Somewhat representative of the average in the HCC patients (non-random sampling) . 1 score

c) Selected demographic group of users. 0 score

d) No description of the sampling strategy. 0 score

2) Sample size:

a) Justified and satisfactory (≥ 400 HCC included). 1 score

b) Not justified (<400 HCC patients included). 0 score

3) Non-Response rate

a) The response rate is satisfactory (≥95%). 1 Score

b) The response rate is unsatisfactory (<95%), or no description. 0 Score

4) Ascertainment of the screening/surveillance tool:

a) Validated screening/surveillance tool. 2 scores

b) Non-validated screening/surveillance tool, but the tool is available or described. 1 score

c) No description of the measurement tool. 0 score

Comparability: (Maximum 1 stars)

1) The potential confounders were investigated by subgroup analysis or multivariable analysis.

a) The study investigates potential confounders. 1 score

b) The study does not investigate potential confounders. 0 score

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. 2 scores

b) Record linkage. 2 scores

c) Self report. 1 score

d) No description. 0 score

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate. 1 score

b) The statistical test is not appropriate, not described or incomplete. 0 score