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ALTERAÇÕES NEUROPSICOLÓGICAS, EMOCIONAIS E COMPORTAMENTAIS EM INDIVÍDUOS INFECTADOS PELO SARS-COV-2

ORIENTADOR: PR. DR. EZEQUIEL BATISTA DO NASCIMENTO

TEIXEIRA DE FREITAS - BA

ABRIL DE 2025

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Dissertação apresentado ao programa de Pós-graduação em Saúde, Ambiente e Biodiversidade pertencente à Universidade Federal do Sul da Bahia, como parte das exigências para obtenção do título de mestre em saúde, ambiente e biodiversidade.

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Este trabalho foi submetido a avaliação e julgado aprovado em: 07 / 04 /2025

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TEIXEIRA DE FREITAS, 2025

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ALTERAÇÕES NEUROPSICOLÓGICAS, EMOCIONAIS E COMPORTAMENTAIS EM INDIVÍDUOS INFECTADOS PELO SARS-COV-2

RESUMO

Pesquisas recentes sugerem uma possível interferência do SARS-CoV-2 no sistema nervoso central, potencialmente associada a alterações em processos cognitivos relatados por indivíduos infectados. No entanto, a variabilidade dessas alterações em componentes específicos das funções executivas, como a velocidade de processamento e o controle cognitivo, ainda é pouco explorada. Considerando a literatura e os diversos quadros clínicos associados à COVID-19, além dos inúmeros relatos de pessoas com queixas cognitivas pós-infecção, decidimos realizar essa pesquisa no extremo sul da Bahia. O objetivo deste estudo é investigar possíveis alterações na velocidade de processamento e no controle cognitivo, bem como seu impacto nos processos de aprendizagem e memória em indivíduos afetados pela infecção por SARS-CoV-2. Trata-se de um estudo observacional, incluindo 52 participantes entre 18 e 60 anos de idade, divididos em três grupos diferentes: sintomáticos (COV-S), controlados (CTL) e hospitalizados (COV-H), recrutados por um questionário sociodemográfico e rastreio clínico, usando vários instrumentos de avaliação ,incluindo o teste De Aprendizagem Auditivo-Verbal De Rey (RAVLT),o inventário Sintomatologia Breve(BSI), o Teste de reconhecimento(TEM-R) e teste de cinco dígitos (FDT), na comunidade do extremo sul da Bahia. Os resultados indicaram que as mulheres do grupo COV-S possuem maior capacidade de retenção de informações em comparação aos homens. O grupo hospitalizado (COV-H) apresentou níveis mais elevados de sensibilidade interpessoal, sintomas obsessivo-compulsivos e ansiedade. Além disso, um nível educacional mais alto foi associado a uma maior eficiência nas funções executivas, especialmente nas áreas de flexibilidade cognitiva e inibição. O SARS-CoV-2 causou desaceleração na velocidade de processamento e prejuízos nas funções executivas, impactando a memória declarativa e a memória de reconhecimento, além de intensificar sintomas obsessivo-compulsivos, ansiedade e sensibilidade interpessoal.

Palavras-chave: velocidade de processamento, Covid-19, Sistema nervosa Central, problemas do comportamento.

NEUROPSYCHOLOGICAL, EMOTIONAL, AND BEHAVIORAL ALTERATIONS IN INDIVIDUALS INFECTED BY SARS-COV-2

ABSTRACT

Recent research suggests a potential interference of SARS-CoV-2 in the central nervous system, possibly associated with alterations in cognitive processes reported by infected individuals. However, the variability of such alterations in specific components of executive functions, such as processing speed and cognitive control, remains underexplored. Considering the existing literature, the diverse clinical conditions associated with COVID-19, and the numerous reports of post-infection cognitive complaints, we chose to conduct this research in the extreme south of Bahia, Brazil. The aim of this study is to investigate potential alterations in processing speed and cognitive control, as well as their impact on learning and memory processes, in individuals affected by SARS-CoV-2 infection. we conduct an observational study, including 52 participants between 18 and 60 years old divided into three different groups: symptomatic (COV-S), controlled (CTL) and hospitalized (COV-H), recruiting by a sociodemographic and screening questionnaire, using several assessment tools , including the Rey Auditory Verbal Learning Test (RAVLT), Brief Symptom Inventory (BSI), Recognition memory test (TEM-R), and Five-Digit Test (FDT), in the extreme south of Bahia community. The results indicated that women in the COV-S group had a greater capacity to retain information compared to men. The hospitalized group (COV-H) showed higher levels of interpersonal sensitivity, obsessive-compulsive symptoms, and anxiety. Additionally, a higher educational level was associated with greater efficiency in executive functions, particularly in cognitive flexibility and inhibition. SARS-CoV-2 induced a decline in processing speed and impairments in executive functions, affecting declarative memory and recognition memory, while also intensifying obsessive-compulsive symptoms, anxiety, and interpersonal sensitivity.

Keywords: processing speed, Covid-19, Central Nervous System, behavioral changes.

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ACE2	Receptor da enzima conversora de angiotensina 2
ALT	Aprendizagem ao longo das Tentativas
BSI	Inventário Sintomatologia Breve
CONEP	Comissão Nacional de Ética em Pesquisa
COV-H	Covid Hospitalizados
COV-S	Covid Sintomáticos
CTL	Controle
FDT	Five Digit Test (Teste dos Cinco Dígitos)
HTLV-1	Vírus linfotrópico da célula humana
IL	Interleucina
IP-10	Interferon gamma-induced protein 10
MCP-3	Proteína quimiotática de monócitos-3
OMS	Organização Mundial da Saúde
RAVLT	Teste De Aprendizagem Auditivo-Verbal De Rey
SNC	Sistema Nervoso Central.
TCLE	Termo de Consentimento Livre e Esclarecido
TEM-R	Teste de Memória de Reconhecimento
UFSB	Universidade Federal Do Sul Da Bahia

SUMÁRIO

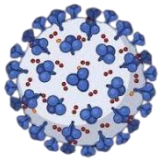
INTRODUÇÃO GERAL

No final do ano 2019, em Wuhan, na China, surgiu o vírus SARS-CoV-2, vírus de moderada transmissibilidade. Dados sugerem o mercado de frutos do mar de Hunan como o foco que primeiro manifestou casos de COVID-19 (LI et al, 2020) e testes realizados em amostras ambientais no mercado de Hunan confirmaram a presença do vírus (Xinhua, 2020). Alguns estudos atestam que o ser humano poderia ter sido contaminado pelo consumo de pangolim, contaminados através de morcegos que funcionavam como reservatórios de SARS-CoV-2 (LAM et al., 2020). Em 11 de Março, a Organização Mundial da Saúde (OMS) decretou estado pandêmico devido ao altíssimo número de infectados em todo o mundo, além dos óbitos. Antes mesmo da declaração por parte da OMS sobre a pandemia vigente, o Brasil já havia registrado o 1° caso de infecção por COVID-19 do país, na data 26 de fevereiro 2020 (OLIVEIRA et al., 2020).

Os vírus "Coronavírus" são encapsulados e possuem um dos maiores genomas entre os vírus com RNA de cadeia única e sentido positivo. Este vírus foi denominado como "Coronavírus" por sua aparência de coroa em seu invólucro, sendo este constatado por meio de microscópio eletrônico. Os coronavírus são pertencentes a subfamília Orthocoronavirinae; família Coronaviridae; ordem Nidovirinaes(CAROD-ARTAL, 2020). Os coronavírus podem ocasionar diversas complicações para a saúde humana, sendo capazes de infectar, além do homem, aves e mamíferos como os morcegos, felinos, roedores etc. Além do SARS-CoV-2, outros tipos de coronavírus também podem infectar o ser humano, como é o caso do: alfacoronavírus 229E e NL63; betacoronavírus HKU1 e OC43; coronavírus associado a síndrome respiratória aguda grave (SARS-CoV) e coronavírus associado a síndrome respiratória do Oriente Médio (MERS-CoV) (DUARTE et al., 2020). O período de incubação do vírus é de cinco dias (média entre 3-7 dias, com no máximo 14 dias). Durante a fase de replicação viral, os indivíduos podem apresentar sintomas leves, isso se deve à consequência do efeito do vírus e da resposta imunológica.

As alterações patológicas das vias respiratórias inferiores sucedem-se quando o sistema imune não consegue frear a propagação e a replicação do vírus e os sintomas respiratórios surgem devido à consequência do efeito citopático sobre as células do pulmão. As primeiras manifestações clínicas da COVID-19 são: febre, tosse seca, dispneia e estresse respiratório agudo. Muitos infectados podem ser assintomáticos ou apresentar sintomas leves, como cefaleia, tosse não produtiva, fadiga, mialgias e anosmia. A mortalidade global estima-se em 8%, e se deve, em grande parte, a insuficiência respiratória com hipóxia ou falência múltipla dos órgãos (CAROD-ARTAL, 2020).

A Organização Mundial da Saúde (OMS, 2023) declarou o fim do status de emergência de saúde pública relacionado à COVID-19. No entanto, as consequências da infecção pelo SARS-CoV-2 ainda persistem em parte da população, sendo denominadas síndrome pós-COVID ou COVID longa (NALBANDIAN et al., 2021). A COVID longa, e a síndrome pós-covid, referem-se a novos sintomas que surgem e persistem por pelo menos 12 semanas após a fase aguda da infecção (Figura 1**).** Segundo a OMS (2020), os sintomas mais frequentemente relatados incluem fadiga, dispneia e comprometimento cognitivo, os quais impactam de forma significativa a vida diária dos indivíduos. Tais manifestações podem permanecer desde o início da infecção, surgir após a recuperação clínica ou apresentar um padrão flutuante, com recaídas ao longo do tempo.



Possível Síndrome De Cuidados Pós-Intensivos Concomitante (PICS)

Sintomas cognitivos: Diminuição da memória, dificuldade em falar, esquecimento, falta de concentração e resolução de problemas

Sintomas afetivos: Depressão, ansiedade, doença da síndrome pós-traumática, diminuição da motivação

Sintomas físicos: fraqueza muscular, fadiga, diminuição da mobilidade, dificuldade em respirar

	COVID aguda		Pós-covid	Covid Longa
Sintomas	Exposição ao SARS-CoV	**Pulmões** Dispneia, tosse, dor no peito **Coração** Palpitações; miocárdica, inflamação **Cérebro** Brain fog, fadiga, delírio, distúrbio do sono, sintomas afetivos **Trato gastrointestinal** Diarreia, náusea **Rim** Compromissos renais, lesão renal aguda	**Pulmões** Dispneia, tosse **Coração** Palpitações; dor no peito **Cérebro** Brain fog/Deficiências cognitivas, fadiga, delírio, distúrbio do sono, sintomas afetivos, depressão, ansiedade, doença da síndrome pós-traumática, má qualidade de vida, fraqueza muscular **Rim** Doença renal crônica **Outro**	Comprometimento da saúde mental e física
	1-4 semanas		**4-12 semanas**	**a partir da 12ª semana**

Figura 1. Apresentação dos sintomas da Covid longa, conforme Bertuccelli et al. (2022).

MECANISMO DE INFECÇÃO DO SISTEMA NERVOSO POR SARS-COV-2

Embora o mecanismo ainda não esteja completamente elucidado, a via olfatória neuronal representa uma importante porta de entrada para vírus respiratórios com potencial neurotrópico, como o SARS-CoV-2, no Sistema Nervoso Central. Estudos demonstraram a presença do vírus no fluido cerebrospinal de pacientes que sofrem de uma forma aguda de SARS-CoV-2 (BAIG et al,2020). Os vírus podem migrar, infectando terminações nervosas sensoriais ou motoras, alcançando transporte neuronal retrógrado ou anterógrado através das proteínas motoras, dineína e cinesinas (SWANSON E MCGAVERN, 2015). O SARS-CoV-2 sofre mutações contínuas em seu material genético, o que poderia contribuir para a variabilidade da evolução neuropatológica.

O SARS-CoV-2 apresenta maior afinidade de ligação ao receptor da enzima conversora de angiotensina 2 (ACE 2) (WRAPP et al., 2020). A hipótese mais provável é que a entrada do SARS-CoV-2 nas células humanas seja mediada pela interação da proteína Spike do vírus com esse receptor, cuja expressão é observada em diversos tecidos, incluindo o epitélio das vias aéreas, pulmões, plexo coroide e várias células cerebrais, como as células endoteliais do sistema microvascular cerebral (PELLEGRINI et al., 2020).

A organização anatômica única dos nervos olfatórios e do bulbo olfatório na cavidade nasal e no prosencéfalo, efetivamente os torna um canal entre o epitélio nasal e o SNC (KOYUNCU et al., 2013). Como consequência, o SARS-CoV-2 pode entrar no cérebro através do trato olfatório nos estágios iniciais da infecção (DESFORGES et al., 2019; MORI, 2015). Depois que o SARS-CoV-2 infecta as células nasais pode atingir todo o cérebro e o líquido cefalorraquidiano através dos nervos olfatório e do bulbo olfatório e causar inflamação e reação desmielinizante (WAN et al.,2021). Também foram encontradas partículas do vírus SARS e sequências de genoma em neurônios cerebrais (EMMI et al.,2023).

Um número crescente de relatos de casos e séries descreve uma ampla gama de manifestações neurológicas em um total de 901 pacientes, mas muitos têm detalhes insuficientes, refletindo o desafio de estudar esses pacientes. Dentre estas manifestações, a encefalopatia foi relatada em 93 pacientes, incluindo 16 (7%) de 214 pacientes hospitalizados com COVID-19 em Wuhan, China e 40 (69%) de 58 pacientes em terapia intensiva com COVID-19 na França. A encefalite foi descrita em oito pacientes até o momento e a manifestação da síndrome de Guillain-Barré em 19 pacientes. O SARS-CoV-2 foi detectado no LCR de alguns pacientes. Anosmia e ageusia são comuns e podem ocorrer na ausência de outras

características clínicas. Inesperadamente, a doença cerebrovascular aguda também está emergindo como uma complicação importante, com estudos de coorte relatando acidente vascular cerebral em 2–6% dos pacientes hospitalizados com COVID-19 (ELLUL et al.,2020).

Outra linha de investigação aponta que a infecção com o SARS-CoV-2 pode causar patologia cerebral por meio de potenciais mecanismos diretos e indiretos (PERON, 2023). Evidências indicam que a infecção pelo SARS-CoV-2 pode desencadear tempestades de citocinas, um fenômeno caracterizado pela liberação excessiva de mediadores inflamatórios (ALI, 2020; SONG et al., 2020). Yang et al, (2020) sugerem que a interleucina (IL) -1ra, IL-6, proteína quimioatraente de monócitos (MCP)-3 e proteína sérica induzida por interferon gama (IP)-10 estão implicados nos desfechos fatais da infecção por COVID-19. Essas tempestades de citocinas podem comprometer a barreira hematoencefálica, permitindo a migração viral para o sistema nervoso central (SNC) e afetando o funcionamento normal dos circuitos neuronais, resultando em possíveis danos neurológicos diretos.

É notório que uma grande parte da população mundial enfrenta desafios relacionados à saúde mental. Além disso, os efeitos a longo prazo da infecção pelo SARS-CoV-2, conhecidos como COVID longa, têm sido alvo de muitos estudos, os quais apontam para uma ampla gama de manifestações. Ariza et al. (2023), em um estudo observacional, mencionam que a COVID-19 pode causar disfunção executiva ao afetar o hipotálamo e favorecer a propagação da infecção para o córtex pré-frontal. Especula-se que as alterações na cognição, emoção e comportamento possam estar relacionadas a modificações distintas em diferentes áreas cerebrais, particularmente nas regiões límbicas envolvidas, como a amígdala, o hipocampo e o córtex pré-frontal (RODRIGUES, 2022; ROZENTHAL et al., 2004).

Em um estudo de neuroimagem, foram observadas alterações microestruturais e funcionais no hipocampo de pacientes pós-agudos com COVID-19, uma região do cérebro essencial para os processos de aprendizagem e memória, além de impactos identificados em uma rede de estruturas do lobo frontal envolvidas nas respostas a reatividade emocional e estresse (STĘPIEŃ et al,2023). O córtex pré-frontal é responsável por controlar o fluxo de informações e ajustar o comportamento, bem como as emoções, de acordo com as demandas ambientais. Em um modelo cognitivo proposto pelas funções executivas, essa área está envolvida em processos controlados, incluindo memória de trabalho, inibição, fluência, flexibilidade cognitiva, raciocínio e autorregulação, que atuam na modulação da cognição e do comportamento. Além disso, o córtex pré-frontal também participa ativamente dos processos de aprendizagem e memória (CARLSON et al., 2013).

Os processos mnemônicos se dividem em vários sistemas de acordo com características temporais, como memória de curto e longo prazo, e características referentes à natureza das informações. Por exemplo, as memórias implícitas ou não-declarativas estão envolvidas em informações sensório-motoras e ocorrem com pouca volição e consciência. Já as memórias declarativas ou explícitas envolvem a aprendizagem de informações conceituais e temporais, contribuindo para mecanismos de percepção e consciência (HARVEY, 2019).

Sabe-se que as memórias relacionadas à formação de conceitos e eventos dependem do hipocampo, que desempenha um papel fundamental na memória declarativa. Esta é dividida em duas componentes: a memória semântica, que envolve o conhecimento geral, e a memória episódica, que se refere às memórias de eventos específicos (BOUYEURE E NOULHIANE, 2020).

Dentre as alterações cognitivas relacionadas à COVID-19, a mais evidenciada clinicamente diz respeito às dificuldades de recuperação de palavras. Isso pode se manifestar como uma dificuldade para encontrar a palavra certa durante uma conversa ou ao escrever, bem como dificuldades em lembrar eventos específicos ou experiências pessoais. Esse quadro pode incluir esquecer compromissos, não conseguir lembrar detalhes de conversas recentes ou não recordar eventos. Esse conjunto de sintomas foi evidenciado em diferentes estudos clínicos e ficou conhecido como "brain fog", ligado à deterioração das memórias declarativas. Acredita-se que esses sintomas possam ser causados por uma combinação de fatores, incluindo a resposta inflamatória do corpo à infecção, os efeitos diretos do vírus no cérebro e o estresse físico e psicológico associado à doença (VELICHKOVSKY et al., 2023).

O impacto da COVID-19 no cérebro, particularmente no que diz respeito à velocidade de processamento, tem sido objeto de extensas pesquisas e pode estar relacionado às alterações cognitivas mencionadas. Vários estudos destacam que a COVID-19 pode levar a comprometimentos cognitivos, relacionados à perda na velocidade de processamento de informações, que é um componente crítico da função cognitiva adequada. Essas mudanças estão frequentemente associadas a um espectro mais amplo de déficits cognitivos observados em sobreviventes da COVID-19, incluindo aqueles com sintomas de COVID longa (VAKANI et al., 2023). Em um estudo recente, 27,3% dos pacientes não hospitalizados com COVID longa e "brain fog" apresentaram comprometimento cognitivo na velocidade de processamento. O estudo encontrou que quase 70% dos pacientes tinham comprometimentos cognitivos objetivos, destacando a velocidade de processamento como uma das funções cognitivas mais afetadas. Isso sugere que indivíduos em recuperação da COVID-19 podem experimentar dificuldades

notáveis em tarefas que exigem processamento cognitivo rápido (CHUANG et al., 2025). Outro estudo indicou que a COVID-19 está associada a uma função cognitiva mais baixa e conectividade funcional alterada no cérebro, o que pode impactar a velocidade de processamento. Especificamente, indivíduos com histórico de COVID-19 demonstraram uma eficiência local significativamente reduzida e hipoconectividade em várias regiões do cérebro, correlacionando-se com função cognitiva subjetiva e fadiga (KESLER et al., 2024). Essas alterações sugerem que, embora o cérebro possa manter um funcionamento objetivo próximo ao esperado, a eficiência do processamento de informações está comprometida, potencialmente levando a sintomas como "brain fog" e velocidade de processamento mais lenta.

Em uma meta-análise recente (KNAPP et al., 2024) que incluiu dados de 54 estudos, abrangendo 6.676 indivíduos com COVID-19 e 12.986 controles saudáveis, a análise revelou um efeito pequeno, mas significativo, indicando que indivíduos com COVID-19 apresentaram um desempenho ligeiramente pior em medidas cognitivas em comparação com os controles saudáveis. O estudo identificou déficits significativos em vários domínios cognitivos: o efeito mais substancial foi encontrado em tarefas que envolviam velocidade de processamento. Também foi observada uma queda significativa na atenção, aprendizado e memória, linguagem e função executiva.

As observações mencionadas aqui indicam que o SARS-CoV-2 pode invadir o SNC a partir da periferia por meio das vias neuronais (CAROD-ARTAL, 2020) e produzir alterações quadros neuropatológicos seguidos de alterações neurofuncionais, o que poderia explicar o compilados de evidências manifestações neurológicas e psiquiátricas em pessoas contaminadas pelas SARS-COV-2. Diante do exposto, este projeto de pesquisa pretende investigar possíveis alterações neuropsicológicas, emocionais e comportamentais em grupos de indivíduos infectados pelo SARS-CoV-2, e relacionar os possíveis achados com prejuízos na velocidade de processamento e controle cognitivo, bem como seu impacto nos processos de aprendizagem e memória.

JUSTIFICATIVA

A COVID-19 prejudicou a saúde física, mas também revelou problemas significativos na saúde mental. Em um estudo transversal nos EUA com mais de 16.000 indivíduos, Perlis et al. (2022) identificaram um total de 15% de participantes positivos para a COVID-19 que relataram sintomas de COVID longa. Considerando a literatura e os diversos quadros clínicos associados à COVID-19, além dos inúmeros relatos de pessoas com queixas cognitivas pós-infecção, decidimos realizar essa pesquisa no extremo sul da Bahia. Além disso, o levantamento nessa região fornecerá dados valiosos sobre indivíduos afetados pela COVID-19 que desenvolveram distúrbios cognitivos, problemas de atenção, aprendizado, memoria e velocidade de processamento, o que também pode ajudar a responder perguntas comuns sobre a compreensão de transtornos neuropsiquiátricos associados à COVID-19. Além de contribuir para a ampliação do conhecimento científico, essa investigação será benéfica para essa comunidade, a fim de determinar a natureza desses distúrbios e poderá auxiliar na formulação de novas estratégias de cuidado em saúde mental voltadas à melhoria da qualidade de vida dos indivíduos afetados.

OBJETIVOS

OBJETIVO PRINCIPAL

Investigar possíveis alterações neuropsicológicas, emocionais e comportamentais em indivíduos infectados pelo SARS-CoV-2, relacionando esses achados com prejuízos na velocidade de processamento e controle cognitivo, e avaliando seu impacto nos processos de aprendizagem e memória.

OBJETIVOS ESPECÍFICOS

1. Investigar o impacto da gravidade dos sintomas nos desfechos de alterações cognitivas e manifestações de sintomas psiquiátricos.
2. Avaliar o efeito do nível de escolaridade sobre os possíveis prejuízos observados na velocidade de processamento e controle cognitivo.
3. Investigar o efeito preditivo da velocidade de processamento e controle cognitivo sobre os processos de aprendizagem e memória.

ARTIGO

EVIDENCE OF IMPAIRED PROCESSING SPEED AND COGNITIVE CONTROL VARIABILITY IN RECOVERED COVID-19 PATIENTS: IMPLICATIONS FOR COGNITIVE DEFICITS AND PSYCHIATRIC RISK

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EVIDENCE OF IMPAIRED PROCESSING SPEED AND COGNITIVE CONTROL VARIABILITY IN RECOVERED COVID-19 PATIENTS: IMPLICATIONS FOR COGNITIVE DEFICITS AND PSYCHIATRIC RISK

ABSTRACT

The COVID-19 pandemic has profoundly impacted cognitive and emotional health, with various studies highlighting both immediate and long-term effects. Cognitive impairments, such as memory issues, and emotional disturbances have been frequently reported among COVID-19 survivors. This study investigates the hypothesis that COVID-19 survivors may exhibit impaired processing speed and cognitive control, which are crucial components of cognitive functioning. These impairments, particularly affected by COVID-19, may underlie learning and memory deficits as well as emotional and behavioral disturbances. An observational study was conducted with 52 participants (age: 35.7 ± 8.7 years, 53% female and 47% male), categorized into three groups: control (CTL), COVID symptomatic (COV-S), and hospitalized (COV-H). Participants were recruited through a sociodemographic and screening questionnaire and assessed using multiple cognitive and psychological evaluation tools, including the Rey Auditory Verbal Learning Test (RAVLT), Brief Symptom Inventory (BSI), Recognition memory test (TEM-R), and Five-Digit Test (FDT). Results indicate that women in the COV-S group outperformed men in information retention. Participants in the COV-H group exhibited heightened interpersonal sensitivity, obsessive-compulsive symptoms, and anxiety. Additionally, a higher level of education was associated with greater efficiency in executive functions, particularly cognitive flexibility and inhibitory control. Overall, SARS-CoV-2 infection appears to negatively impact processing speed and executive functions, leading to impairments in declarative and recognition memory while also increasing symptoms of obsessive-compulsive behavior, anxiety, and interpersonal sensitivity.

Keywords: Long Covid, Brain fog, Cognitive impairment, working memory.

INTRODUCTION

The COVID-19 pandemic has impacted not only physical health but also the cognitive functions and mental health of those infected. Previous studies have shown that various SARS-CoV-2 variants, including Alpha, Beta, Delta, and Omicron, may lead to neurocognitive impairments (Prabhakaran et al., 2023; Spinicci et al., 2022; Taquet et al., 2020). Emerging research suggests these cognitive impairments primarily affect attention, working memory, and processing speed (Vakani et al., 2023). Working memory enables the temporary storage and manipulation of information (Tan et al., 2025), while processing speed refers to the rate at which cognitive tasks are executed (Bouchard, 2025). However, there is considerable variability in findings, with some studies suggesting that cognitive impairments are more pronounced in individuals with mild to moderate symptoms. Approximately 20-40% of survivors with mild-to-moderate COVID-19 developed cognitive impairments (Henneghan et al., 2022).

According to the National Institute for Health and Care Excellence (NICE) guidelines, "*Long COVID*" refers to symptoms that persist or emerge beyond four weeks after the acute phase of COVID-19, without an alternative medical explanation. Among the most concerning symptoms of long COVID are cognitive impairments, commonly referred to as "*Mental fog"* (Pallanti et al., 2023) or "*Brain fog"*. However, this term is considered imprecise (Rosenberg et al., 2024) and broadly describes issues such as *sluggish thinking* and *cognitive fuzziness* (Sia et al., 2023), which primarily involve deficits in attention, memory, and overall cognitive function most frequently observed in clinical cases of long COVID (Denno et al., 2025) The presence of SARS-CoV-2 in the brain has been confirmed through post-mortem analyses and in vitro models using brain organoids (Song et al., 2021; Matschke et al., 2020).

SARS-CoV-2 can induce brain pathology through both direct and indirect mechanisms (Peron, 2023). Evidence suggests that SARS-CoV-2 infection can trigger a cytokine storm, a phenomenon characterized by the excessive release of inflammatory mediators (Ali, 2020; Song et al., 2020). The continuous mutations in the virus's genetic material may contribute to the variability of its neuropathological effects. SARS-CoV-2 exhibits a high binding affinity for the angiotensin-converting enzyme 2 (ACE2) receptor (Wrapp et al., 2020).Prevailing evidence suggests that the virus enters human cells through the interaction of the Spike protein with ACE2, which is abundantly expressed in the epithelium of the airways and lungs, as well as in the choroid plexus and various brain cells, including endothelial cells of the cerebral microvascular system (PELLEGRINI et al., 2020) .Once SARS-CoV-2 infects nasal cells, it

can spread to the brain and cerebrospinal fluid via the olfactory nerves and olfactory bulb, leading to inflammation and a demyelinating response (Wan et al., 2021).

While evidence supports post-COVID-19 cognitive deficits, the variability in executive functions such as processing speed and cognitive control remains underexplored. The short- and long-term neuropsychiatric effects of COVID-19 are closely linked to the cognitive impairments observed in long COVID (Butler et al.,2020). A Systematic review of 27 studies conducted by Crivelli et al. (2022) identified deficits in executive function, attention, and memory in individuals with long COVID-19 (mean age 56.06 years), persisting from the acute phase up to 7 months post-infection. Most studies primarily assess the overall impact of COVID-19 on cognition without examining dynamic fluctuations in cognitive performance, which could reveal more subtle dysfunctions or patterns of cognitive recovery (Fineschi et al., 2024; Guillén et al., 2024; Möller et al., 2023). Additionally, few studies investigate the potential link between cognitive variability and an increased risk of psychiatric manifestations, such as anxiety and depression (Hamza et al., 2025; Shi et al., 2020; Yuan et al., 2022). The complex and multifaceted nature of long COVID contributes to the difficulty in drawing definitive conclusions regarding the long-term cognitive and emotional vulnerabilities experienced by survivors (Tabacof et al., 2022). In an observational study, Ariza et al. (2023) reported that COVID-19 may lead executive dysfunction by affecting the hypothalamus and facilitating viral spread to the prefrontal cortex. Chuang et al. (2025) suggest that cognitive deficits in patients with long COVID primarily affect the ventral prefrontal cortex, rather than the dorsolateral prefrontal cortex, especially in tasks related to memory recall and inhibitory control. Ferrucci et al. (2021) demonstrated that 42% of patients with COVID-19 experience deceleration in cognitive processing speed.

While the evidence points to significant impacts of COVID-19 on cognitive and emotional impairments, it is essential to consider the influence of processing speed and cognitive control, which are crucial for global cognitive functioning and may underlie learning and memory impairments. These effects are observed in both acute and long-term cases, with varying degrees of severity depending on factors such as gender, education, and the severity of the COVID-19 infection. Hence, we hypothesize that instability in these cognitive processes may be associated with a higher risk of memory impairment and psychiatric symptoms, suggesting that infection-related neural impairment could contribute to deficits in cognitive functioning, emotional regulation, and behavioral changes.

METHODS

PARTICIPANTS AND SAMPLE SIZE

A power analysis was conducted using G*Power (version 3.1.9) to estimate the required sample size adequate for testing comparisons between groups for the hypotheses. Using an estimated power of 95%, an alpha level of 5%, and an effect size of 0.5, the minimum sample size required was determined to be 65 participants (critical F = 3.14). In the evaluated sample composition, a total of 52 participants took part, divided into the control group (CTL, n = 10), symptomatic COVID group (COV-S, n = 30), and hospitalized COVID group (COV-H, n = 12).

GROUPS

For the purposes of comparison and testing the hypotheses addressed in this study, participants were initially divided according to the clinical forms of COVID-19 exposure. The control group (CTL, n = 10) included participants who self-declared not having had a previous diagnosis of COVID-19, as well as those who reported no symptoms but had tested positive for SARS-CoV-2. The COV-S group (n = 30) consisted of participants who experienced flu-like symptoms and had previous contact with an infected person (score > 6), along with self-reported positive tests for SARS-CoV-2. The COV-H group (n = 12) included participants who reported moderate to severe clinical conditions that required hospitalization. For statistical analyses considering the effect of gender, the groups were subclassified as follows: CTL (female, n = 4; male, n = 6), COV-S (female, n = 21; male, n = 9), and COV-H (female, n = 3; male, n = 9)

ETHICAL ASPECTS

This study was approved by the Research Ethics Committee at the Federal University of Southern Bahia (UFSB), no. 4.368.891, in compliance with the guidelines of the National Research Ethics Commission (CONEP) for research involving human subjects. All participants were duly informed on the purposes of the study and signed the informed consent form (ICF).

The study included three participant groups: (1) COVID-Symptomatic (COV-S), comprising individuals aged 18–65 with a confirmed SARS-CoV-2 infection (either a screening score >6 or a positive test); (2) COVID-Hospitalized (COV-H), consisting of participants who required hospitalization due to COVID-19; and (3) Control (CTL), asymptomatic individuals with or without a positive test. Exclusion criteria applied to all groups and involved current psychoactive substance use, prior diagnoses of major depression, dementia, or or post-traumatic stress disorder, impaired consciousness, attention deficits, or generalized anxiety during testing, as well as failure to meet COVID-19 confirmation criteria (e.g., screening score <6, no positive test, or no hospitalization history for COVH).

DATA COLLECTION

PROCEDURES

CLINICAL AND SOCIODEMOGRAPHIC QUESTIONNAIRE

This is a questionnaire adapted from Lu et al. (2020) and was used to characterize participants socially and clinically. The questionnaire includes questions about sociodemographic data, a history of previous clinical conditions, symptoms observed during the acute phase of the infection, neurological symptoms, and treatment used by the participant. Additionally, it incorporates a screening instrument adapted by the São Paulo State Department of Health, in partnership with USP, for research studies on COVID-19. The questionnaire template can be found in the project appendices.

COGNITIVE FUNCTIONING ASSESSMENT

Rey Auditory-verbal learning test (RAVLT)

The RAVLT is a neuropsychological assessment designed to evaluate episodic declarative memory through a list of simple and frequent words in Brazilian Portuguese. It includes immediate recall, delayed recall, and a recognition task, assessing auditory-verbal learning, interference effects, information retention, and recognition memory. The test begins with an initial learning phase in which the examiner reads aloud List A, consisting of 15 unrelated words, at a rate of one word per second. The participant then recalls as many words as possible, in any order, and this process is repeated five times to measure learning progress. Next, the examiner presents List B, a new set of 15 words, which is read aloud once, followed by immediate recall of List B. This step assesses proactive interference, or the effect of previously learned information (List A) on the learning of new information (List B), and retroactive interference, which is assessed later during recall of List A after exposure to List B. This phase provides insight into cognitive flexibility, the ability to adapt to new information, and sensitivity to interference, which are crucial for understanding memory consolidation. Immediately after recalling List B, the participant attempts to recall List A once more, without rereading, to assess short-term memory. After a 20–30-minute delay, the participant is again asked to recall the words from List A, without prior rereading, to assess long-term memory retrieval (Alviarez-Schulze et al., 2022; Malloy-Diniz et al., 2007).

Recognition memory test (TEM-R-2)

The Recognition Memory Test (TEM-R-2) is a neuropsychological instrument designed to evaluate declarative semantic memory. It offers comprehensive information about the functioning of the semantic system through culturally adapted stimuli for the Brazilian population. The test consists of a series of figures and letters to be memorized by the participant. It is particularly suited for use with elderly individuals presenting mental disorders or neurological diseases, especially those with neurocognitive disorders such as dementia or mild cognitive impairment The TEM-R-2 contributes to both the diagnosis and differential diagnosis of clinical conditions marked by declarative semantic memory deficits. Its administration typically takes around 15 minutes and is not limited by the participant's age or educational background (Rueda, 2012).

Five-digit test (FDT)

The FDT is a validated neuropsychological test based on the *Stroop Color-Word Test* (Stroop, 1935), used to assess processing speed in automatic attentional processes, as well as controlled attentional processes related to cognitive control mechanisms, interference, and flexibility in the manipulation of stimuli (Campos et al., 2016). In this neuropsychological test, participants need to verbally report the stimuli presented in different frames containing 50 items (individual squares with 5 digits, expressed as numbers or asterisks). In the first two subtasks, which evaluate automatic reading and counting processes, the participant must read the numbers within the square, regardless of the quantity. Then, in the counting subtask, the participant must count the number of target stimuli (*) within the square. The third (choice) and fourth (alternation) subtask evaluate controlled processes, which require the participant to mobilize a higher level of cognitive resources for execution. In the choice subtask, the participant must inhibit the reading of the numbers presented and instead indicate how many numbers there are in each incongruently presented stimulus (e.g., if the stimulus presented is 2-2-2, he must count 3 and not read two). In the final step of the subtask, each square containing the digits is bounded by a thicker edge. In this subtask, the participant is instructed to alternate the reading of the number. The stimuli in step 4 are composed of 80% counting stimuli and 20% reading stimuli, reducing the occurrence of attentional response automation and increasing the demand for executive flexibility mechanisms. The inhibition and flexibility ratios are calculated by subtracting the reaction time of the reading subtest from the times of the choice and toggle tasks, respectively. Low values reflect slowness in choice/inhibition and change/flexibility and may be indicative of slowness in cognitive control of executive functions (Paiva et al., 2016).

PSYCHIATRIC OUTCOMES

Brief Symptomatology Inventory (BSI)

The brief symptomatology inventory (BSI) is used to identify the emotional state of the participant at the time of the application of the cognitive tests, a screening inventory of psychological changes will be applied. The Brief Symptom Inventory (BSI) is a self-report inventory, with 53 items organized into 9 symptom scales: (Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). These scales are named to reflect the patterns of psychological symptoms in general and psychiatric patients. Each item of the BSI is rated on a

five-point psychological distress scale (0 to 4), which aims to monitor the progress of treatment and the changes that treatment causes in patients' behaviors and psychological symptoms (Nazaré et al., 2017). The instrument is applied to young people and adults from 12 years of age, with no education restrictions, and its application is carried out in 8 minutes.

STATISTICAL ANALYSIS

The Kolmogorov-Smirnov test was used to assess the normality of the distribution of the variables used in the study. To test the hypothesis of differences between clinical groups, a two-way ANOVA was conducted to analyze the effects of groups, gender, and their interaction on the variance of mean scores for execution time and errors in the FDT tasks, as well as the indices of flexibility and inhibition. The effect of education level was controlled using analysis of covariance (ANCOVA) to determine whether education level influenced task performance. For evaluating group performance on the RAVLT task, a repeated measures ANOVA was used to assess the effect of trials (A1-A5), estimating an ascending learning curve. Additionally, the effects of group differences, gender, and their interaction with trials were evaluated. Differences in the ALT index, retroactive and proactive interference, retention index, short-term and long-term memory recall were assessed using two-way ANOVA for group differences, gender, and interactions. Similarly, for recognition memory evaluated through total scores on the TEM-R test, a two-way ANOVA was used, controlling for the same effects. Psychiatric outcomes were assessed using weighted scores from the BSI scale. Tukey's post hoc corrections were applied for the ANOVA analyses. Multiple linear regression models were conducted to test the predictive effect of processing speed and cognitive control on the learning and encoding processes in the RAVLT task. Effect sizes were estimated using partial eta squared (η^2_p), where $\eta^2_p = 0.01$ indicates a small effect; $\eta^2_p = 0.06$ indicates a medium effect; and $\eta^2_p = 0.14$ indicates a large effect (Lakens, 2013). Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using Statistica 7.0 software for Windows.

RESULTS

SOCIODEMOGRAPHIC CHARACTERIZATION

A structured questionnaire was used to collect clinical and demographic information from participants, covering variables such as age, gender, and education level. Thus, this study included a sample of 52 participants. Details about the descriptive statistics of the sample composition can be observed in Table 1.

Table 1.

Sociodemographic Characteristics of Study Participants

Characteristic	CTL	COV-S	COV-H
Sample Size (n)	10	30	12
Age (Mean ± SD)	37,8 ± 5,8	31,3 ± 8,3	40,6 ± 6,1
Gender			
Male	60%	30%	75%
Female	40%	70%	25%
Education Level			
graduate degree	80%	90%	34%
High school	20%	6%	66%
Elementary school	0%	4%	0%

Note. This table presents the sociodemographic characteristics of study participants, categorized into Control (CTL), symptomatic COVID-19 (COV-S), and hospitalized COVID-19 (COV-H) groups.

AUTOMATIC PROCESS (FIVE DIGIT TEST)

Reading Subtask

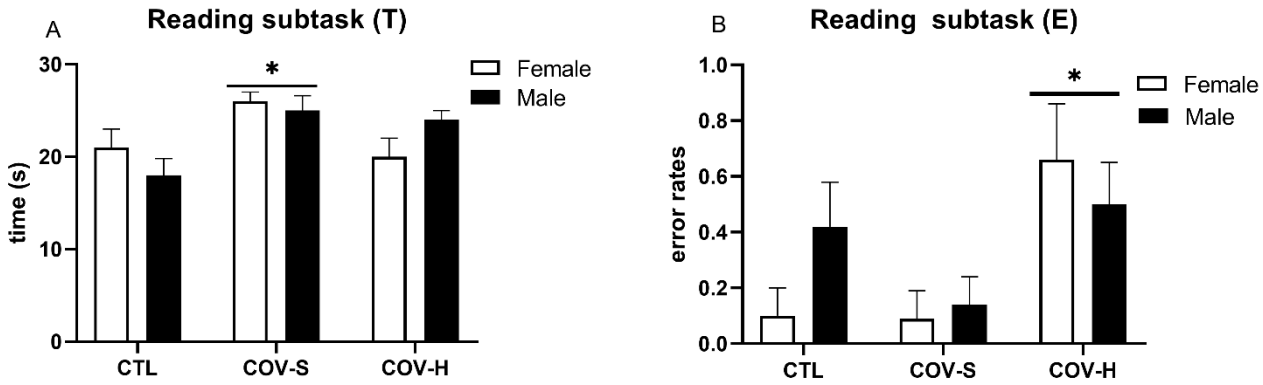
For execution time in the reading subtask, a two-way analysis of variance (ANOVA) revealed significant differences between groups [$F(46,2) = 6.22$, $p = 0.004$, $\eta^2_p = 0.21$], but no significant effects for gender [$F(46,1) = 0.08$, $p = 0.92$] or the interaction between gender and groups [$F(46,2) = 1.32$, $p = 0.27$]. Post-hoc Tukey correction indicated that the COV-S group took longer to complete the task compared to the control group, suggesting a reduction in processing speed for this specific task (Figure 2). Additionally, the ANCOVA analysis did not reveal a significant effect of education level on task completion time [$F(45,1) = 1.00$, $p = 0.32$].

Regarding error rates in the reading subtask, a two-way ANOVA revealed a significant group effect [$F(45,2) = 4.69$, $p = 0.01$, $\eta^2_p = 0.17$], but no significant differences for gender [$F(45,1) = 0.117$, $p = 0.73$] or the interaction between group and gender [$F(45,2) = 1.47$, $p = 0.18$]. Post-hoc Tukey correction for the observed group effect indicated that the COV-H group

exhibited a higher error rate compared to both the control and COV-S groups, suggesting impairments in error monitoring during task execution (Figure 2). Additionally, ANCOVA analysis did not reveal a statistically significant effect of education level on task performance [$F(45,1) = 0.274$, $p = 0.60$].

Figure 2.

Processing Time and Error Rate in the Reading Subtask Across Groups



Note. Mean task completion time (left) and error rates (right) for the Reading Subtask are displayed across the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. The COV-S group exhibited a longer task completion time compared to the control group (A,*$p < 0,05$), suggesting reduced processing speed. Additionally, the COV-H group showed a higher error rate compared to both the control and COV-S groups, indicating impairments in error monitoring (B, *$p < 0,05$). All data expressed as mean ± SEM.

Counting subtask

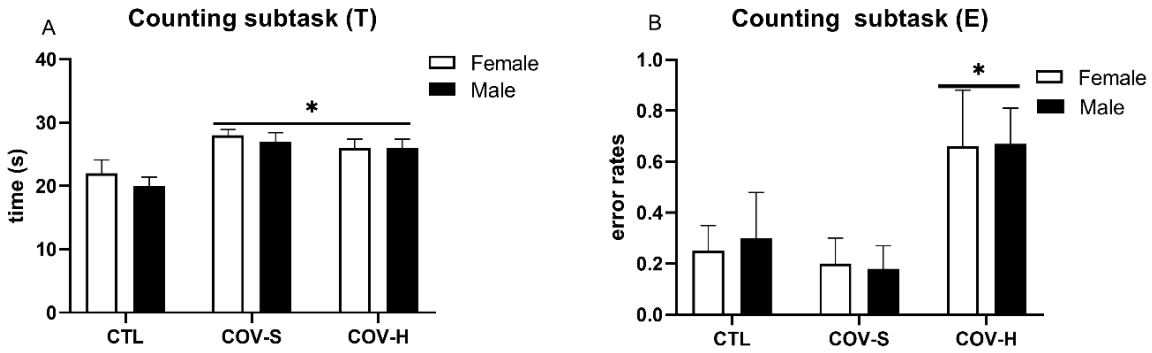
For the counting subtask, a two-way ANOVA revealed a significant group effect on task completion time [$F(45,2) = 7.69$, $p = 0.001$, $\eta^2_p = 0.25$], but no significant differences for gender [$F(45,2) = 0.77$, $p = 0.38$] or the interaction between group and gender [$F(45,2) = 0.70$, $p = 0.92$]. Post-hoc analysis for the observed group effect indicated that both the COV-S and COV-H groups had longer task completion times compared to the control group, suggesting slower execution of this task (Figure 3). Additionally, ANCOVA analysis assessing the impact of education level on processing speed did not reveal statistical significance [$F(45,1) = 0.69$, $p = 0.41$], suggesting that education level did not influence task performance.

Regarding the error rate in the counting subtask, a two-way ANOVA revealed a significant group effect [$F(45,2) = 4.15$, $p = 0.02$, $\eta^2_p = 0.15$], but no significant differences for gender [$F(45,1) = 0.20$, $p = 0.96$] or the interaction between group and gender [$F(45,2) = 0.18$, $p = 0.83$]. Post-hoc analysis for the observed group effect indicated that the COV-H group

exhibited a higher error rate compared to both the control and COV-S groups, suggesting impairments in error monitoring during task execution. Furthermore, ANCOVA analysis did not reveal a significant effect of education level on task performance [F(45,1) = 0.33, p = 0.56].

Figure 3

Processing Time and Error Rates in the Counting Subtask Across Groups



Note. Mean task completion time (left) and error rates (right) for the Counting Subtask across the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. The COV-H and COV-S groups required more time to complete the task compared to the control group (A, * <0,05), suggesting slower processing speed. Additionally, the COV-H group exhibited a higher error rate than both the control and COV-S groups, indicating impairments in error monitoring (B, *< 0,05). All data expressed as mean ± SEM.

CONTROLLED PROCESSES (FIVE DIGIT TEST)

Choice subtask

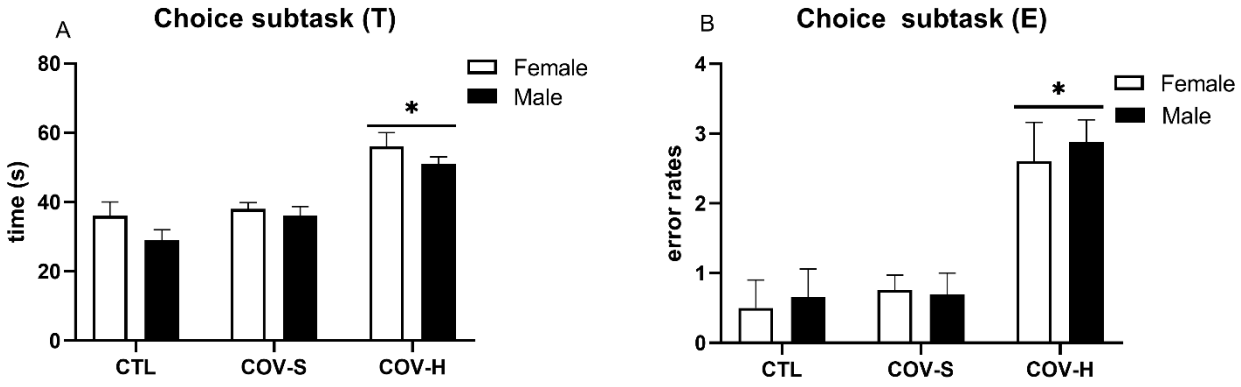
When analyzing task completion time for the choice subtask, a two-way ANOVA revealed a significant group effect [F(45,2) = 9.30, p = 0.0001, η^2_p = 0.28], but no significant effects for gender differences [F(45,1) = 1.98, p = 0.16] or the interaction between group and gender [F(45,2) = 0.54, p = 0.54]. Post-hoc Tukey correction for the observed group effect indicated that the COV-H group took longer to complete the task compared to both the control and COV-S groups, suggesting impairments in processing speed (Figure 4). Additionally, ANCOVA analysis assessing whether education level influenced task performance did not reveal statistical significance [F(45,1) = 2.95, p = 0.09], suggesting that the observed deficits were not related to education level.

Regarding the error rate in choice subtask execution, the statistical analysis revealed a significant group effect [F(45,2) = 7.48, p = 0.001, η^2_p = 0.24], but no significant differences for gender [F(45,1) = 0.25, p = 0.61] or the interaction between group and gender [F(45,2) = 0.37, p = 0.77]. Post-hoc analysis for the group effect indicated that the COV-H group exhibited

a higher error rate compared to both the control and COV-S groups (Figure 4). Additionally, ANCOVA analysis revealed statistical significance [F(45,1) = 4.49, p = 0.03, η^2_p = 0.09], suggesting that higher education levels tend to reduce error rates across groups.

Figure 4

Processing Time and Error Rate in the Choice Subtask Across Groups



Note. Mean task completion time (left) and error rates (right) for the Choice Subtask across the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. The COV-H group exhibited a longer task completion time compared to both the control and COV-S groups, suggesting impairments in processing speed (A, *p < 0,05). Additionally, the COV-H group demonstrated a higher error rate than the other groups (B, *p < 0,05). ANCOVA analysis indicated that education level was a significant factor, suggesting that higher education levels tend to reduce error rates. All data expressed as mean ± SEM.

Alternation subtask

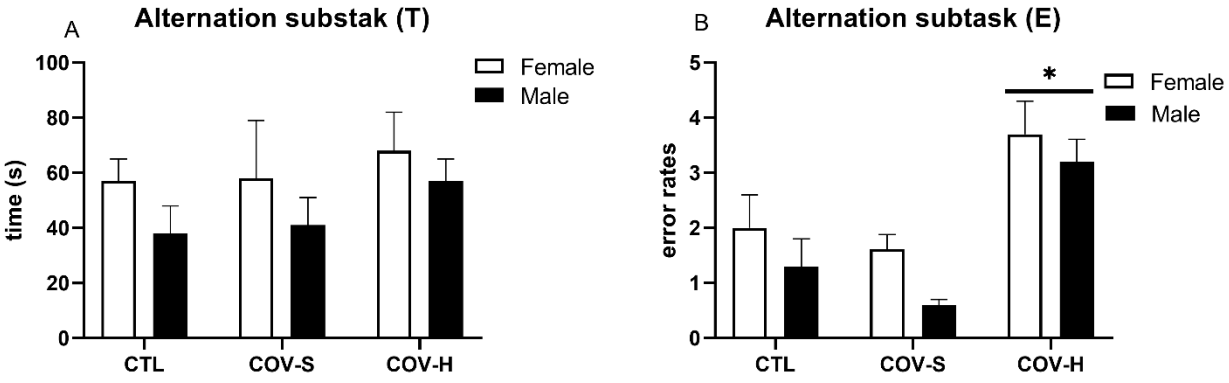
Regarding task completion time for the alternation subtask, a two-way ANOVA did not reveal a significant group effect [F(45,2) = 1.26, p = 0.29], nor significant differences for gender [F(45,1) = 1.19, p = 0.29] or the interaction between group and gender [F(45,2) = 0.96, p = 0.38]. However, ANCOVA analysis indicated a significant effect of education level on task execution [F(45,1) = 25.03, p = 0.001, η^2_p = 0.37], suggesting that higher education levels positively influence task completion time.

Regarding the error rate in task execution, a two-way ANOVA revealed a significant group effect [F(45,2) = 3.45, p = 0.04, η^2_p = 0.14], but no significant differences for gender [F(45,1) = 1.80, p = 0.18] or the interaction between group and gender [F(45,2) = 0.52, p = 0.56, η^2_p = 0.02]. Post-hoc Tukey correction indicated that hospitalized individuals (COV-H) had higher error rates compared to both the control and COV-S groups, suggesting impairments

in error monitoring during task execution (Figure 5). Additionally, ANCOVA analysis revealed statistical significance [F(45,1) = 8.51, p = 0.005, η^2_p = 0,16], suggesting that higher education levels may enhance task performance.

Figure 5

Processing Time and Error Rate in the Alternation Subtask Across Groups



Note. Mean task completion time (left) and error rates (right) for the Alternation Subtask across the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. No significant differences were observed between groups in task completion time (A). However, the COV-H group exhibited a higher error rate compared to both the control and COV-S groups, suggesting impairments in error monitoring (B, *p < 0,05). Additionally, ANCOVA analysis indicated that education level had a significant effect, suggesting that higher education levels contribute to better task performance. All data expressed as mean ± SEM.

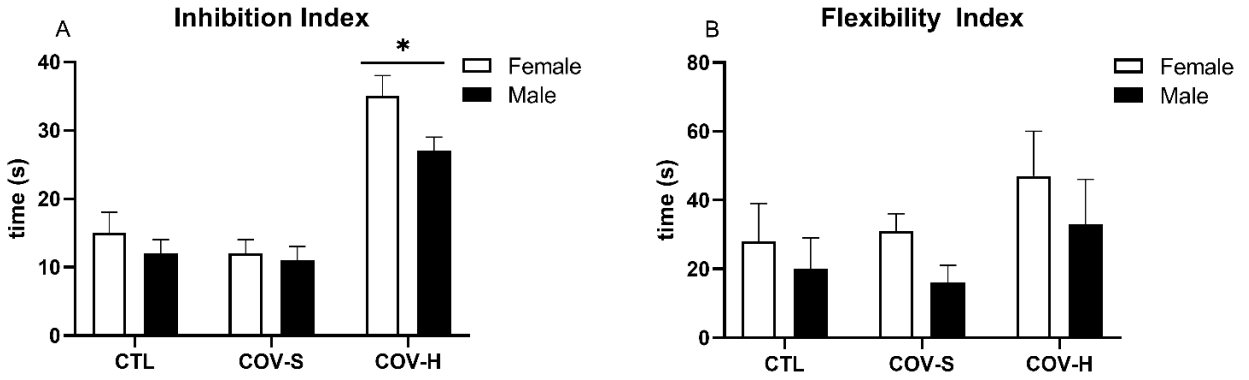
EXECUTIVE FUNCTIONS INDEX

This study investigated the presence of impairments in cognitive control, specifically in executive functioning indices of inhibition and flexibility, as measured by the FDT task. Regarding the inhibition index, statistical analysis revealed a significant group effect [F(45,1) = 16.97, p = 0.001, η^2_p = 0.43], but no significant effects for gender [F(45,1) = 2.91, p = 0.09] or the interaction between group and gender [F(45,2) = 0.94, p = 0.39]. Post-hoc Tukey correction indicated that the observed group effect was driven by slower efficacy of inhibition processes in the COV-H group compared to both the control and COV-S groups (Figure 6). Additionally, ANCOVA analysis revealed a significant effect of education level on this index [F(45,1) = 3.97, p = 0.05, η^2_p = 0.08], suggesting that higher education levels may mitigate potential impairments in inhibition performance.

Regarding the flexibility index, statistical analysis did not reveal a significant effect for group differences [F(45,2) = 0.60, p = 0.54], gender [F(45,1) = 1.20, p = 0.27], or the interaction between group and gender [F(45,2) = 0.66, p = 0.51]. However, ANCOVA analysis indicated a significant effect of education level on the flexibility index [F(45,1) = 26.9, p = 0.0001, η^2_p = 0.37], suggesting that higher education levels contribute to improved efficiency of flexibility (Figure 6).

Figure 6

Inhibition and Flexibility Indices Across Groups



Note. Mean performance scores for inhibition (left) and flexibility (right) indices across the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. The COV-H group exhibited slower inhibition processes, as indicated by longer response times in the inhibition index compared to the control and COV-S groups (A, *p <0,05). No significant differences were observed between groups for the flexibility index. However, ANCOVA analysis indicated a significant effect of education level on both indices, suggesting that higher education levels contribute to improved cognitive flexibility and may mitigate potential deficits in inhibition. All data expressed as mean ± SEM.

LEARNING AND MEMORY (REY AUDITORY VERBAL LEARNING TEST)

Acquisition processes

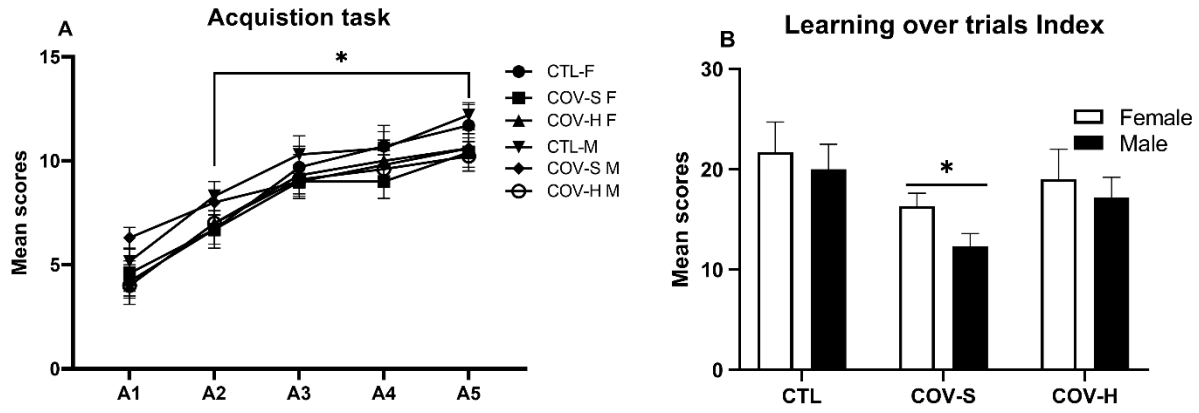
The study investigated the effect of COVID-19 exposure on the acquisition process of the RAVLT task. A repeated-measures ANOVA revealed a significant learning effect across trials [F(184,4) = 93.87, p = 0.0001, η^2_p = 0.67], but no significant interaction effects for trials × groups [F(184,8) = 1.61, p = 0.12], trials × gender [F(184,4) = 0.76, p = 0.52], or trials × groups × gender [F(184,8) = 0.25, p = 0.97]. Additionally, the analysis showed no significant differences between groups [F(46,2) = 0.85, p = 0.43], gender [F(46,1) = 1.13, p = 0.29], or the interaction between groups and gender [F(46,2) = 0.46, p = 0.63]. Post-hoc Tukey correction for the trial effect indicated a progression in the ability to recall the word list over trials,

suggesting a learning curve across all conditions. This finding implies that COVID-19 exposure did not impact the acquisition process of the task (Figure 7).

The study analyzed the LOT index, an estimate of learning efficiency throughout the test while controlling for the effect of the first trial. A two-way ANOVA revealed a significant group effect [$F(45,2) = 4.75$, $p = 0.01$, $\eta^2_p = 0.17$], but no significant effects for gender differences [$F(45,1) = 0.69$, $p = 0.40$] or the interaction between group and gender [$F(45,2) = 0.90$, $p = 0.90$]. Post-hoc analysis indicated that participants in the COV-S group exhibited lower scores compared to the control group, suggesting a reduction in learning efficiency across trials (Figure 7).

Figure 7

Learning Curve Across Trials and Learning Over Trials Index in the RAVLT



Note. The left graph shows the mean number of words learned by each group across the five trials, while the right graph presents the mean scores of the Learning Over Trials (LOT) index for the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. A significant trial effect was observed, with the number of words learned in the last four trials being higher than in the first trial (A, $*p < 0.05$). Regarding the LOT index, Tukey's post-hoc test revealed a reduction in this index for the COV-S group compared to the control group (B, $*p < 0.05$). All data are expressed as mean ± SEM.

Memory Encoding

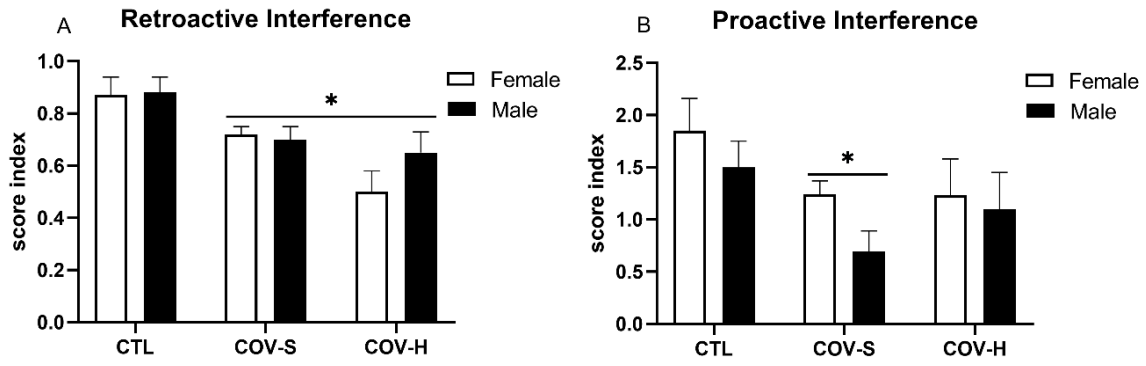
The study investigated differences between groups regarding retroactive interference, proactive interference, and the rate of forgetting in the memory encoding process. Concerning the retroactive interference index, which assesses the susceptibility of information from the first list being impaired by exposure to list B, the statistical analysis revealed a significant group effect [$F(45,2) = 7.64$, $p = 0.001$, $\eta^2_p = 0.25$]. However, no significant differences were observed

between genders [F(45,1) = 0.76, p = 0.76] or in the interaction between groups and gender [F(45,2) = 1.01, p = 0.37]. Tukey's post-hoc test indicated that the COV-S and COV-H groups had significantly lower scores compared to the control group, suggesting that, after exposure to list B, these groups lost part of the content previously learned. Furthermore, the ANCOVA analysis did not reveal significant statistical differences [F(45,1) = 0.10, p = 0.98], indicating the absence of an effect of education level on this process.

Regarding proactive interference, which estimates the susceptibility of new information (List B) to be impacted by exposure to previously presented content, the statistical analysis revealed a significant group effect [F(45,2) = 1.87, p = 0.01, η^2_p = 0.17]. However, no significant differences were observed between genders [F(45,2) = 1.84, p = 0.18] or in the interaction between groups and gender [F(45,2) = 0.74, p = 0.47]. Post-hoc analysis indicated that the COV-S group had a reduced score compared to the control group, suggesting that this group exhibits greater fragility in the ability to encode new information (Figure 8). Similarly, the ANCOVA analysis did not reveal an effect of education level on this process [F(45,1) = 0.37, p = 0.54].

Figure 8

Retroactive and Proactive Interference Across Groups in the RAVLT Task



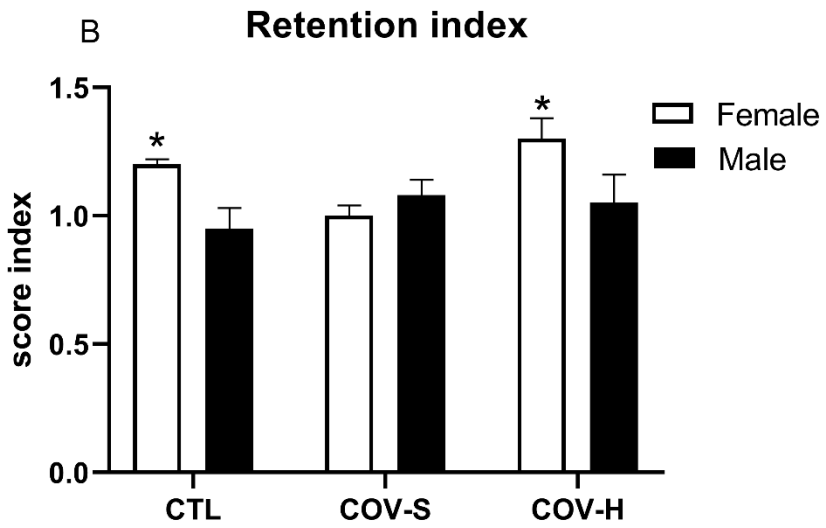
Note. The mean scores of retroactive interferences for the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. A significant group effect was observed, with the COV-S and COV-H groups showing lower scores compared to the control group (A, *p <0.05). For proactive interference, statistical analysis observed lower scoring of COV-S group when compared to control group. Error bars represent the standard error of the mean (B, *p < 0.05). All data are expressed as mean ± SEM.

Regarding the retention index, the statistical analysis revealed a significant interaction effect between groups and gender [F(45,2) = 3.45, p = 0.04, η^2_p = 0,13], as well as significant differences between genders [F(45,1) = 4.09, p = 0.04, η^2_p = 0.08]. However, no significant

group effect was observed [F(45,2) = 2.22, p = 0.12]. Post-hoc analysis for the interaction effect indicated differences between genders in the control and COV-H groups, where male participants exhibited lower scores. This difference was not observed in the COV-S group (Figure 9), suggesting that women have a better ability to retain learned content over time and with exposure to distractors. Additionally, the study found no effect of education level on the forgetting rate [F(45,1) = 0.13, p = 0.25].

Figure 9

Retention index Across Groups in the RAVLT Task



Note. The graph illustrates the mean retention index for the CTL (Control), COV-S (COVID-Symptomatic) and COV-H (COVID-Hospitalized) groups. A significant interaction effect between groups and gender was observed, with male participants in the control and COV-H groups showing lower scores compared to female participants. This difference was not present in the COV-S group. All data are expressed as mean ± SEM.

MEMORY RECALL PROCESSES(REY AUDITORY VERBAL LEARNING TEST)

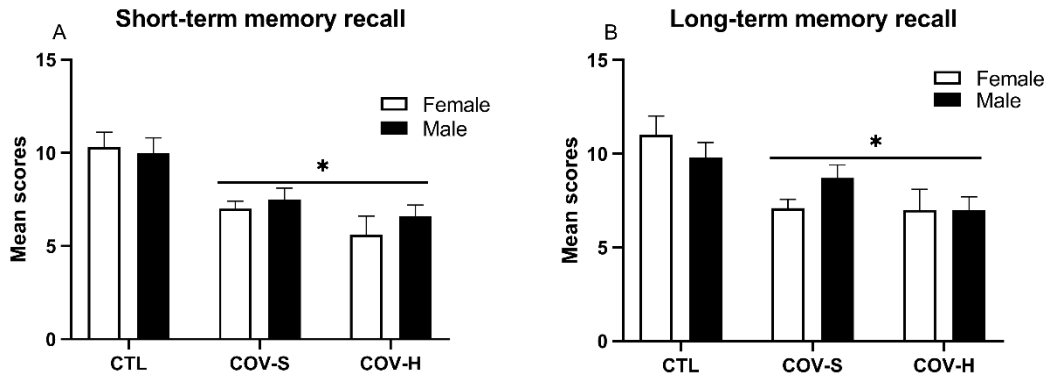
The study investigated differences between groups regarding the retrieval processes in the task, considering both short-term memory and long-term memory. For short-term memory, the statistical analysis using a two-way ANOVA revealed a significant group effect [F(45,2) = 9.04, p = 0.001, η^2_p = 0.28], but no significant differences were found between genders [F(45,1) = 0.72, p = 0.40] or in the interaction between groups and gender [F(45,2) = 0.23, p = 0.79]. Tukey's post-hoc test indicated that both the COV-S and COV-H groups demonstrated a reduced capacity for immediate recall, as evidenced by a lower number of words remembered (Figure 10). Additionally, we investigated whether education level could influence performance in

immediate recall, but no statistical significance was observed in the ANCOVA analysis [F(45,1) = 0.17, $p = 0.67$].

Regarding long-term memory retrieval, the two-way ANOVA analysis revealed a significant group effect [F(45,2) = 7.05, $p = 0.002$, $\eta^2_p = 0.23$], but no significant effects were found for gender [F(45,1) = 0.13, $p = 0.71$] or in the interaction between groups and gender [F(45,2) = 0.70, $p = 0.50$]. Tukey's post-hoc correction for group effects indicated that the COV-S and COV-H groups had lower mean scores for word recall 20 minutes after the last recall, suggesting impairments in long-term memory retrieval (Figure 10). Furthermore, the ANCOVA analysis did not reveal an effect of education level on delayed recall [F(45,2) = 0.83, $p = 0.36$].

Figure 10

Short-Term and Long-Term Memory Recall Across Groups in the RAVLT Task



Note. The mean scores of short-term and long-term memory recall for the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. A significant group effect was observed, with both the COV-S and COV-H groups demonstrating lower scores compared to the control group (A, *$p < 0.05$). For long-term memory recall, statistical analysis revealed that the COV-S and COV-H groups had significantly lower recall scores 20 minutes after the last recall compared to the control group (B, *$p < 0.05$). All data are expressed as mean ± SEM.

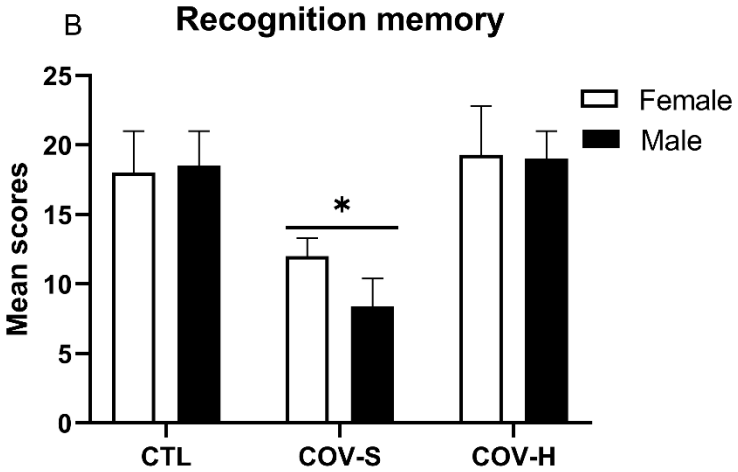
RECOGNITION MEMORY (RECOGNITION MEMORY TEST)

Regarding recognition memory, which refers to the ability to identify a stimulus or situation as familiar based on prior encounters, the Recognition Memory Test (TEM-R) was utilized. The statistical analysis using a two-way ANOVA revealed a significant group effect [F(45,2) = 9.72, $p = 0.001$, $\eta^2_p = 0.30$], but no significant differences were found between genders [F(45,1) = 0.37, $p = 0.55$] or in the interaction between groups and gender [F(45,2) = 0.65, $p = 0.52$]. Tukey's post-hoc analysis indicated that the COV-S group exhibited poorer recognition scores compared to both the COV-H and control groups, suggesting that impairments in recognition memory may be specific to mild and moderate cases of COVID-19

(Figure 11). Additionally, the ANCOVA analysis did not reveal an effect of education level on task performance [F(45,1) = 0.32, p = 0.57].

Figure 11

Recognition Memory Scores Across Groups in the TEM-R



Note. The graph illustrates recognition memory scores for the CTL (Control), COV-H (COVID-Hospitalized), and COV-S (COVID-Symptomatic) groups. A significant group effect was observed, with the COV-S group showing lower recognition scores compared to both the COV-H and control groups (*p < 0.05). All data are expressed as mean ± SEM.

PYSCHIATRIC OUTCOMES (BRIEF SYMPTOM INVENTORY)

The study investigated differences between groups concerning psychiatric symptom manifestations using the Brief Symptom Inventory (BSI). Symptoms related to anxiety, worries, and exposure to traumatic experiences were assessed through the domains of anxiety, somatization, phobic anxiety, and obsessive-compulsive symptoms. Additionally, mood and affective changes were measured by interpersonal sensitivity, hostility, and depressive symptoms. Manifestations related to psychotic symptoms were evaluated through paranoid ideation and psychoticism.

For anxious symptoms, the two-way ANOVA revealed a significant group effect [F(46,2) = 3.52, p = 0.03, η^2_p = 0.13], but no significant differences were found between genders [F(45,1) = 0.55, p = 0.46] or in the interaction between groups and gender [F(45,2) = 0.78, p = 0.46]. Tukey's post-hoc correction indicated that the COV-H group reported a higher occurrence of anxious symptoms compared to the COV-S and control groups, with no differences between the COV-S and control groups regarding anxious symptom reports. This suggests a greater manifestation of symptoms in individuals exposed to COVID-19 and hospitalized (Table 2).

Regarding phobic anxiety, the statistical analysis did not reveal significant differences between groups [F(46,2) = 2.17, p = 0.12], gender differences [F(46,1) = 0.04, p = 0.83], or interaction effects between groups and gender [F(46,2) = 0.04, p = 0.95]. For somatization symptoms, the two-way ANOVA analysis did not reveal significant differences between groups [F(46,2) = 1.25, p = 0.29], nor between genders [F(46,1) = 0.48, p = 0.48], or in the interaction between groups and gender [F(46,2) = 0.12, p = 0.88]. These findings indicate that there are no occurrences of symptoms of somatization among the evaluated groups.

For obsessive-compulsive symptoms, the statistical analysis revealed a significant group effect [F(46,2) = 9.68, p = 0.003, η^2_p = 0.29], but no significant differences were found for gender [F(46,1) = 0.34, p = 0.56] or interaction effects between groups and gender [F(46,2) = 0.13, p = 0.87]. Post-hoc testing showed that the COV-H group had higher scores for obsessive-compulsive symptom manifestations compared to the COV-S and control groups, with no differences between the COV-S and control groups, suggesting that obsessive-compulsive symptoms may occur mostly in hospitalized patients (Table 2).

The statistical analysis of interpersonal sensitivity symptoms revealed significant differences between groups [F(46,2) = 5.05, p = 0.01, η^2_p = 0.18], but no differences were found between genders [F(46,1) = 0.97, p = 0.32] or in the interaction between groups and gender [F(46,2) = 0.17, p = 0.85]. Post-hoc analysis indicated a higher prevalence of interpersonal sensitivity manifestations in the COV-H group compared to the COV-S and control groups, with no differences observed between the COV-S and control groups, suggesting that these alterations are related to hospitalized patients (Table 2). In contrast, the two-way ANOVA for hostility behaviors did not reveal significant differences for group effects [F(46,2) = 1.42, p = 0.24], gender effects [F(46,1) = 1.02, p = 0.31], or in the interaction between groups and gender [F(46,2) = 0.39, p = 0.67]. These results indicate that the expression of hostility behaviors did not vary across the groups. Similarly, the analysis of depressive symptoms showed no significant differences for group effects [F(46,2) = 2.75, p = 0.07], gender effects [F(46,1) = 0.18, p = 0.41], or in the interaction between groups and gender [F(46,2) = 0.86, p = 0.86]. These findings suggest that there are no differences in the manifestations of depressive symptoms among the groups (Table 2).

Regarding the manifestations of psychotic symptoms, the statistical analysis using a two-way ANOVA for paranoid ideation did not reveal significant differences between groups [$F(46,2) = 1.22$, $p = 0.30$], nor between genders [$F(46,1) = 1.17$, $p = 0.31$], or in the interaction between groups and gender [$F(46,2) = 0.42$, $p = 0.79$]. Similarly, the two-way ANOVA analysis for other psychotic symptoms also showed no significant group effects [$F(46,2) = 1.29$, $p = 0.28$], no significant gender differences [$F(46,1) = 2.26$, $p = 0.13$], or interaction effects between groups and gender [$F(46,1) = 0.81$, $p = 0.44$]. These findings suggest that there are no differences among the groups regarding the manifestations of psychotic symptoms (Table 2).

Table 2

Weighted Scores of BSI Domains by Group

Psychiatric Symptoms	CTL F	CTL M	COV-S F	COV-S M	COV-H F	COV-H M
ANX	0,27 ± 0,2	0,22 ± 0,2	0,45 ± 0,12	0,36 ± 0,18	**1,1 ± 0,18***	**0,66 ± 0,3***
PHOB	0,15 ± 0,3	0,11 ± 0,2	0,55 ± 0,13	0,65 ± 0,2	0,60 ± 0,3	0,67 ± 0,2
SOM	0,15 ± 0,3	0,15 ± 0,2	0,45 ± 0,15	0,71 ± 0,23	0,30 ± 0,4	0,55 ± 0,4
OC	0,19 ± 0,3	0,26 ± 0,2	0,59 ± 15,1	0,87 ± 0,23	**1,60 ± 0,23***	**1,65 ± 0,40***
IS	0,7 ± 0,2	0,13 ± 0,2	0,39 ± 0,12	0,68 ± 0,19	**0,83 ± 0,32***	**1,05 ± 0,19***
HOST	0,20 ± 0,2	0,16 ± 0,2	0,24 ± 0,11	0,42 ± 0,17	0,40 ± 0,3	0,80 ± 0,17
PI	0,15 ± 0,3	0,11 ± 0,2	0,55 ± 0,13	0,65 ± 0,21	0,60 ± 0,3	67,7 ± 0,2
PSYC	0,14 ± 0,1	0,10 ± 0,5	0,28 ± 0,12	0,60 ± 0,18	0,13 ± 0,3	0,72 ± 0,18

Note. The weighted scores for the different domains of the Brief Symptom Inventory (BSI) for both females and males across all groups. The two-way ANOVA analysis with Tukey correction revealed a significant increase in self-reported symptoms in the COV-H (COVID-Hospitalized) group for the domains of anxiety, obsessive-compulsive (OC), and interpersonal sensitivity (IS) compared to the CTL (Control) and COV-S (COVID-Symptomatic) groups. Data are expressed as mean and standard deviation (SD).

MULTIPLE LINEAR REGRESSION MODELS ASSESSING THE IMPACT OF PROCESSING SPEED AND COGNITIVE CONTROL ON ACQUISITION AND ENCODING PROCESSES OF RAVLT

The study investigated the hypothesis that impairments in processing speed and cognitive control could impact the acquisition an encoding process of RAVLT. To assess this, we utilized execution times from the FDT subtask —including reading, counting, choice, and alternation—to infer processing speed (Model I). Additionally, we employed inhibition and flexibility indices to evaluate cognitive control in relation to the ALT index (Model II). This analysis aimed to explore the influence of processing speed impairments, as well as inhibition and flexibility indices, on performance in the ALT index. The study also tested the hypothesis that processing speed and cognitive control influence the memory encoding process in the RAVLT task, specifically evaluating the retroactive interference index, which showed statistical significance for both clinical groups. To assess this, Model III examined the execution times of FDT subtasks as measures of processing speed, evaluating their predictive effect on retroactive interference index. In Model IV, inhibition and flexibility indices were tested as predictors of retroactive interference performance, to assess the role of cognitive control in memory encoding effects.

A multiple linear regression analysis was conducted to evaluate the predictive effect of the execution time of FDT subtasks (model I), as an independent variable of processing speed, on the acquisition task, estimated by the ALT index. The model I was statistically significant, explaining 46.3% of the variance in ALT index [Adjusted $R^2 = 0.463$, $F(6, 45) = 8.33$, $p = 0.001$].

Among the predictors, the time of reading was a significant predictor of the ALT index [$\beta = -0.642$, $t(45) = -2.71$, $p = 0.009$], indicating that for each 1-second increase in reading time, there was an estimated reduction of 0.64 points in the ALT index. This suggests that longer execution time, an indicator of slower processing speed in the reading task, reflects slower learning of the word lists. However, the execution time in the counting task [$\beta = -0.264$, $t(45) = -1.10$, $p = 0.27$), choice task [$\beta = 0.15$, $t(45) = 0.12$, $p = 0.27$], and alternation task [$\beta = -0.07$, $t(45) = -0.18$, $p = 0.85$] did not significantly predict acquisition performance, indicating that these parameters may not influence verbal learning memory. Additionally, the model considered clinical group status as a predictor for the outcomes in the ALT index, using the control group as the reference level. The model observed no significant effects for the COV-S condition [β =

-2.63, t(45) = -1.21, p = 0.22] or the COV-H condition [β = -3.28, t(45) = -1.19, p = 0.24], suggesting that these conditions may not strongly explain performance in the acquisition task (Table 3).

Regarding Model II, we used multiple linear regression analysis to estimate the influence of flexibility and inhibition indices on performance in the ALT index. The statistical analysis revealed that the model was statistically significant, explaining 21% of the variance in the ALT index [Adjusted R^2 = 0.210, F(4, 47) = 4.40, p = 0.004].

Analyzing the predictor variables, neither the inhibition index [β = 0.150, t(47) = 0.90, p = 0.32) nor the flexibility index (β = -0.017, t(47) = -0.49, p = 0.62) showed statistically significant predictive effects on the ALT index. However, when considering clinical groups, using the control group as the reference, the model found a significant effect for the COV-S group [β = -7.75, t(47) = -3.71, p = 0.001], suggesting that this clinical condition reduces the ALT index by 7.75 points (Table 3). For the COV-H group, the observed impact was a reduction of 6.17 points in the ALT index, although this relationship was observed as a statistical trend (β = -6.17, t(47) = -1.90, p = 0.06).

Considering the predictive effect of processing speed on retroactive interference, the linear regression analysis revealed that the model III was statistically significant, explaining 35% of the observed variance in the interference index (Adjusted R^2 = 0.356, F(6, 45) = 5.57, p = 0.001). When evaluating the predictive effect of the variables in the model III, no statistically significant effects were observed for the execution time of the reading task (β = 0.10, t(45) = 1.74, p = 0.09), counting task (β = -0.104, t(45) = -1.15, p = 0.18), choice task (β = -0.05, t(45) = -1.35, p = 0.18), or alternation task (β = -0.83, t(45) = 0.76, p = 0.44).

However, when testing the predictive effect of clinical condition as a predictor variable, statistically significant effects were observed for the COV-S group (β = -0.183, t(45) = -2.73, p = 0.009), indicating that the symptomatic COVID condition reduces the retroactive interference index by 0.18 points. This suggests greater vulnerability in encoding new information due to previous stimuli. Similarly, a statistically significant effect was observed for the hospitalized COVID condition (β = -0.24, t(45) = -2.59, p = 0.01), suggesting that the hospitalized COVID condition may reflect a reduction in the retroactive interference index, indicating greater vulnerability in encoding new information.

In Model IV, testing the effect of cognitive control, the multiple linear regression analysis revealed statistical significance, explaining 42% of the observed variance in the retroactive interference index (Adjusted $R^2 = 0.420$, $F(4, 47) = 10.2$, $p = 0.001$).

Considering the predictive effects of the variables, the inhibition index was statistically significant ($\beta = -0.12$, $t(47) = -3.12$, $p = 0.003$), suggesting that an increase in this index, which reflects slower inhibitory capacity, could reduce the retroactive interference scores by 0.12 points. This indicates that impairments in inhibitory control increase difficulties in encoding new information. However, the flexibility index did not show statistical significance as a predictor ($\beta = 0.01$, $t(47) = 1.52$, $p = 0.13$).

When considering clinical conditions as predictor variables, the model found statistical significance for the COV-S group ($\beta = -0.21$, $t(47) = -4.00$, $p = 0.001$) and the COV-H group ($\beta = -0.17$, $t(47) = -2.03$, $p = 0.04$), suggesting that, compared to the control group, these conditions could reduce the retroactive interference index by 0.21 and 0.17 points, respectively. This finding indicates that COVID conditions may negatively impact the process of encoding new information (Table 3).

Table 3

Multiple Linear Regression Analysis of the Impact of Processing Speed and Cognitive Control on Acquisition and Encoding Processes in the RAVLT

Models	**ALT index**		
Model I (Processing speed x acquisition process)	**(α)**	**(β)**	**R^2**
Reading (t)	35.17	**-0.642**	**0.463***
Counting (t)		-0.264	0.463
Choice (t)		0.150	0.463
Alternation (t)		-0.07	0.463
COV-S condition		-2.63	0.463
COV-H condition		-3.28	0.463
Model II (Cognitive control x acquisition process)	**ALT index**		
	(α)	**(β)**	**R^2**
Inhibition index	20.80	0.150	0.210
Flexibility index		-0.017	0.210
COV-S condition		-7.75	**0.210***
COV-H condition		-6.17	**0.210***
Model III (Processing speed x encoding process)	**Retroactive Interference**		
	(α)	**(β)**	**R^2**
Reading (t)	1.05	0.10	0.356
Counting (t)		-0.10	0.356
Choice (t)		-0.05	0.356
Alternation (t)		-0.83	0.356
COV-S condition		-0.183	**0.356***
COV-H condition		-0.24	**0.356***
Model IV (Cognitive control x encoding process)	**Retroactive Interference**		
	(α)	**(β)**	**R^2**
Inhibition index	1.04	**-0.12**	**0.420***
Flexibility index		0.01	0.420
COV-S condition		-0.21	**0.420***
COV-H condition		-0.17	**0.420***

Note. This table presents the results of multiple linear regression analyses predicting the processing speed and cognitive control over the acquisition and encoding process index. Model I tested the predictive effect of processing speed, measured by execution times of FDT subtasks, on the ALT index. Model II tested the predictive effect of cognitive control, measured by inhibition and flexibility indices, on the ALT index. Model III examined the predictive effect of processing speed on retroactive and proactive interference indices. Model IV tested the predictive effect of cognitive control on retroactive interference index. Statistically significant predictors are indicated *$p < 0.05$. The data are expressed as regression coefficients (β), t-values and regression constant (α).

DISCUSSION

Our study explored how impairments in processing speed and cognitive control might contribute to learning and memory deficits and psychiatric symptoms, particularly in individuals affected by different clinical outcomes of COVID-19. We aimed to observe processing speed and cognitive impairment across the clinical severity of COVID-19 through the performance of learning and memory processes, as well as the impact on psychiatric manifestations. Additionally, we controlled for well-recognized factors such as gender and educational level, which are relevant variables to consider in COVID-19 cognitive impairment.

Our initial findings observed impairments in execution time for automatic processes such as reading and counting. Interestingly, the slowing of reading processing speed was more robust in participants from the COV-S group, with no statistical difference for the COV-H group. However, we observed a higher occurrence of errors in the COV-H group, suggesting a greater prevalence of failures in cognitive control mechanisms. This evidence suggests a dissociative response, with the COV-S group showing a loss in processing speed without impacting error monitoring capacity, i.e., without impacting cognitive control. In the counting test, when evaluating execution time, we also observed a loss in processing speed in both groups, but only the COV-H group showed impairments in the ability to self-monitor errors. This suggests that the severity of COVID-19 may elicit impairments in processing speed and cognitive control in more severe cases, such as those requiring hospitalization.

In relation to controlled processes, which by their nature demand more cognitive resources, the brain needs to mobilize a broader and more sophisticated network of cognitive resources to achieve precise and efficient task execution. Our data observed impairments in processing speed in the choice Subtask and impairments in monitoring capacity in both the choice and alternation subtasks in the COV-H group. This evidence suggests that severe COVID-19 cases with hospitalization impact processing speed and cognitive control, indicating impairments in the neural networks related to executive functions (Chuang et al., 2025; Crivelli et al., 2022; Tabacof et al., 2022). Indeed, when analyzing the inhibition index, we observed impairments in the inhibition capacity of participants in the COV-H group, with longer times in this index, suggesting a slowing in this component of executive functioning. The findings of this study provide strong evidence that COVID-19 negatively affects cognitive control and executive functions, particularly processing speed, cognitive flexibility, and inhibition. Moreover, previous studies have demonstrated that clinical conditions significantly affect

semantic memory, episodic memory, processing speed, and executive function (Ariza et al., 2023; Almería et al., 2024).

It is noteworthy that the ANCOVA analysis, which assessed the influence of educational level on processing speed and cognitive control, revealed statistical significance only for errors in controlled processes, as well as for indices of cognitive flexibility and inhibition. These findings suggest that the deleterious effects of COVID-19 on executive functions may differ according to educational background, indicating that a higher educational level could serve as a protective factor. One possible explanation for this observation lies in the cognitive reserve hypothesis. Cognitive reserve refers to the brain's ability to compensate for structural damage by engaging alternative neural networks to maintain cognitive performance (Stern, 2002). In line with this hypothesis, Cian et al. (2022), in a study conducted in Italy with 45 patients who had been hospitalized for COVID-19 and recovered from the acute phase without requiring ICU admission, found no significant differences in cognitive outcomes based on age, gender, or educational level.

In our study, we evaluated the potential impairments of COVID-19 on learning and memory processes using the RAVLT, a well-recognized task for assessing components of episodic memory in an auditory-verbal context. Initially, we assessed the impact of clinical conditions on the acquisition process. We observed that exposure to COVID-19 did not alter the ability to learn the word list over the trials, suggesting integrity in the acquisition process of the presented content. However, in the ALT index, which evaluates learning capacity without the influence of the first exposure (which could be facilitated by recency and primacy effects), we observed impairments in the ALT index for the COV-S group. This suggests that this group exhibits slower learning, requiring more trials to reinforce the learned information. These findings suggest that the acquisition stage may be minimally affected by COVID-19. It is known that in the learning stage, the efficiency of processing speed, the level of arousal (i.e., the state of alertness), and the integrity of sensory and perceptual circuits are fundamental elements for the acquisition process. The quality of neural pathways that process sensory information (such as vision, hearing, and touch) ensures that stimuli are represented accurately and robustly. This contributes to more effective encoding of experiences and, consequently, the formation of more durable memories (Histed, 2025).

The COVID-19 pandemic has been associated with a range of sensory-perceptual symptoms, particularly affecting the senses of smell and taste, as frequently reported in anosmia and dysgeusia symptoms. A study testing impairment in sensory areas found evidence

reinforcing sensory and perceptual deficits in taste and smell. However, the study found that vestibular and auditory functions were rarely affected (Ludwig et al., 2022). This evidence suggests that auditory-verbal processing does not seem to be impacted by COVID-19, which may explain the minimal impairments observed in the acquisition stage of the RAVLT task.

Regarding the encoding stage, we evaluated potential impairments through interference indices and the ability to retain learned content. In this phase, the recently formed memory is quite labile, making it vulnerable to interference, such as when exposed to another distractor word list (Moyano et al., 2022).

Regarding the retroactive interference index, we observed that the COV-S and COV-H groups had lower scores in this index, suggesting that their ability to retain already consolidated information (List A) was impaired after exposure to List B. We found that the control group was able to remember almost 90% of the words from the first list after exposure to the distractor list, whereas the COV-S and COV-H groups had a percentage recall estimate ranging from 60% to 70% for the first list after exposure to the distractor list. This suggests that retroactive interference impairs the encoding stage in these groups and may be related to COVID-19 exposure. Concerning proactive interference, the COV-S group showed a reduced score compared to the control group, indicating that their ability to retain words from List B was impaired by the prior exposure to List A, suggesting more lability in encoding processes.

Regarding retention capacity and the vulnerability of content to retention, our study did not reveal an impact of COVID-19 exposure on the rate of retention. However, a gender effect was observed, with women showing better retention indices and a lower occurrence of information loss over time. This gender-dependent effect was also observed in the interaction with clinical groups, where women in the control and COV-H groups scored better than men. This suggests a trend for gender differences as a variable that may influence performance in cognitive tasks evaluated in patients exposed to COVID-19. Indeed, evidence indicates that women outperform men in verbal episodic memory tasks, which involve recalling words and stories. In a prospective longitudinal cohort study, Alviarez-Schulze et al. (2022) found gender to be a statistically significant predictor of long-term forgetting in RAVLT performance, with women recalling more words spontaneously than men. This advantage is attributed to women's superior verbal production abilities, which enhance their performance in tasks requiring verbal processing (Herlitz & Rehnman, 2008; Reifegerste et al., 2021).

Considering the impact of COVID-19 exposure on the recall process, our study investigated the effects on short-term and long-term memory recall in the RAVLT. Our findings observed impairments in both the COV-S and COV-H groups, demonstrating a reduced capacity for immediate recall and later recall, 20 minutes after the task ended, suggesting persistent impairments in episodic memory.

In this study, we evaluated recognition memory using the Recognition Memory Test (TEM-R) to assess the ability to identify familiar stimuli based on prior encounters. A two-way ANOVA revealed a significant group effect, indicating that the COV-S group showed poorer recognition scores compared to both the COV-H and control groups. In contrast, Bertuccelli et al. (2022) conducted a scoping review on cognitive impairment in individuals with a history of COVID-19 infection and reported that visual and spatial abilities are rarely affected. This discrepancy highlights potential differences in the cognitive domains affected by COVID-19, with our study suggesting that recognition memory may be more severely impacted in individuals who experienced severe illness.

In our sample, the hospitalized COVID-19 group (COV-H) presented higher levels of interpersonal sensitivity, obsessive-compulsive symptoms and anxiety, which are factors commonly associated with executive functioning. However, these findings contrast with those of Cian et al. (2022), who reported significantly higher scores on the state anxiety scale in the control group.

In our study, we also evaluated the impact of COVID-19 on the manifestation of psychiatric symptoms. In our sample, the hospitalized COVID-19 group (COV-H) exhibited higher levels of self-reported symptoms of anxiety, interpersonal sensitivity, and obsessive-compulsive symptoms. One possible hypothesis for the higher occurrence of psychiatric manifestations in COV-H patients is that hospitalization may have been a stressor or traumatic event, leading to alterations in the activation of limbic structures such as the prefrontal cortex, amygdala, and hippocampus, which are crucially involved in emotion regulation and fear response. Consistent with our data, other studies have observed that hospitalized patients with COVID-19 often experience significant anxiety due to the stress of hospitalization, compounded by the uncertainty and severity of the disease (Goda et al., 2021; Tan et al., 2023). Interestingly, our findings observed impairments in error self-monitoring capacity and the inhibition index in the FDT task, suggesting impairments in executive functioning, which may reinforce the hypothesis of the negative impact of stress on structures involved in emotion and behavioural regulation.

In our study, multiple linear regression analyses revealed significant relationships between processing speed, cognitive control, and memory encoding in individuals affected by COVID-19 through four models. In Model I, we observed that execution time was an indicator of slower processing speed during the reading task. In Model II, we assessed the impact of cognitive flexibility and inhibition on the ALT index, finding that clinical conditions significantly influenced performance, with COV-S showing a stronger negative effect on learning compared to COV-H. In Model III, we found that clinical conditions significantly impacted encoding, with both COV-S and COV-H groups reducing the retroactive interference index, indicating greater vulnerability in encoding new information. Finally, Model IV examined the effect of cognitive control on retroactive interference, showing that clinical conditions significantly affected encoding. Both COV-S and COV-H groups exhibited greater difficulty in encoding new information, as evidenced by reduced retroactive interference indices. These results demonstrate that COVID-19-related cognitive disorders can disrupt the brain's ability to filter out irrelevant information and efficiently encode new memories.

Previous studies, such as that by Ferrucci et al. (2021), corroborate our findings by demonstrating that 42% of patients with COVID-19 experience a decline in cognitive processing speed, evidenced by low scores on the Symbol Digit Modalities Test (SDMT). These cognitive effects are attributed to brain changes directly related to the viral neurotropism of SARS-CoV-2 rather than systemic complications such as hypoxemia. The presence of the virus in the brain has been confirmed in post-mortem studies and in vitro models using brain organoids (Song et al., 2021; Matschke et al., 2020), reinforcing the hypothesis that COVID-19 can cause direct damage to the central nervous system, compromising processing speed and cognitive control.

Other viruses, including HTLV-1, arboviruses, and human herpesviruses, have been associated with cognitive impairments. HTLV-1 (Human T-lymphotropic virus type 1), the first human pathogenic retrovirus identified, is transmitted through unprotected sex, needle sharing, and transfusions, with approximately 1% of infected individuals developing central nervous system disorders like HTLV-1-associated myelopathy/tropical spastic paraparesis (HAM/TSP) (Araújo & Wedemann, 2019). However, a study on HTLV-1 carriers found no association between depression and cognitive disorders in most neuropsychological tests, including the RAVLT (Gascon et al., 2017). Similarly, some arboviruses, like the Chikungunya virus, have been linked to cognitive impairments, affecting executive functions, cognitive flexibility, inhibitory control, and memory (Peixoto et al., 2022). Additionally, human herpesvirus

infections (HSV-1, HSV-1/2, and HSV-2) have been related to cognitive decline, potentially due to infection or reactivation (Shi et al., 2024; Warren-Gash et al., 2019).

This study has some limitations, such as the small sample size, which may compromise the generalizability of the results. Additionally, the age, socioeconomic status, and comorbidities of participants were not assessed, which could have provided more context for interpreting the findings. The use of standardized statistical methods and data, however, strengthens the scientific validity of the results and their applicability to understanding the neuropsychological impacts of COVID-19. Despite these limitations, the study offers valuable insights into how COVID-19 affects cognitive control and executive functions, contributing to a deeper understanding of the long-term cognitive and behavioral consequences of the virus. Future studies with larger, more diverse samples and a broader set of variables would help to validate and expand upon these findings.

In summary, our findings indicate a decline in processing speed and executive functions and is influenced by the clinical condition, whether symptomatic (COV-S) or hospitalized (COV-H). Additionally, participants with a higher level of education scored better on the executive function assessment, while women demonstrated a greater capacity to retain information. The hospitalized group (COV-H) exhibited higher levels of interpersonal sensitivity, obsessive-compulsive symptoms, and anxiety, suggesting that the severity of the infection is associated with more intense cognitive and emotional changes. These findings highlight the importance of considering sociodemographic factors when assessing the cognitive and emotional consequences of COVID-19, underscoring the need for targeted interventions to support recovery in the post-COVID-19 period.

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CONSIDERAÇÕES FINAIS

Os resultados deste estudo fornecem evidências de que a COVID-19 afeta negativamente o controle cognitivo e as funções executivas, especialmente a velocidade de processamento, a flexibilidade cognitiva e a inibição, impactando a aquisição e a codificação da memória. O tempo de execução foi um preditor de lentidão na aquisição de memória, enquanto a flexibilidade cognitiva e a inibição prejudicadas, principalmente em indivíduos com COVID-19 sintomática (COV-S), tiveram um impacto negativo mais pronunciado no aprendizado. Tanto os grupos sintomáticos quanto os hospitalizados demonstraram maior dificuldade em codificar novas informações. Embora as mulheres tenham mostrado melhor retenção de informações que os homens, o grupo hospitalizado apresentou níveis mais elevados de sensibilidade interpessoal, sintomas obsessivo-compulsivos e ansiedade. Além disso, um nível educacional mais alto foi associado a maior eficiência nas funções executivas, reforçando a educação como um fator protetor para a reserva cognitiva.

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ANEXO 1

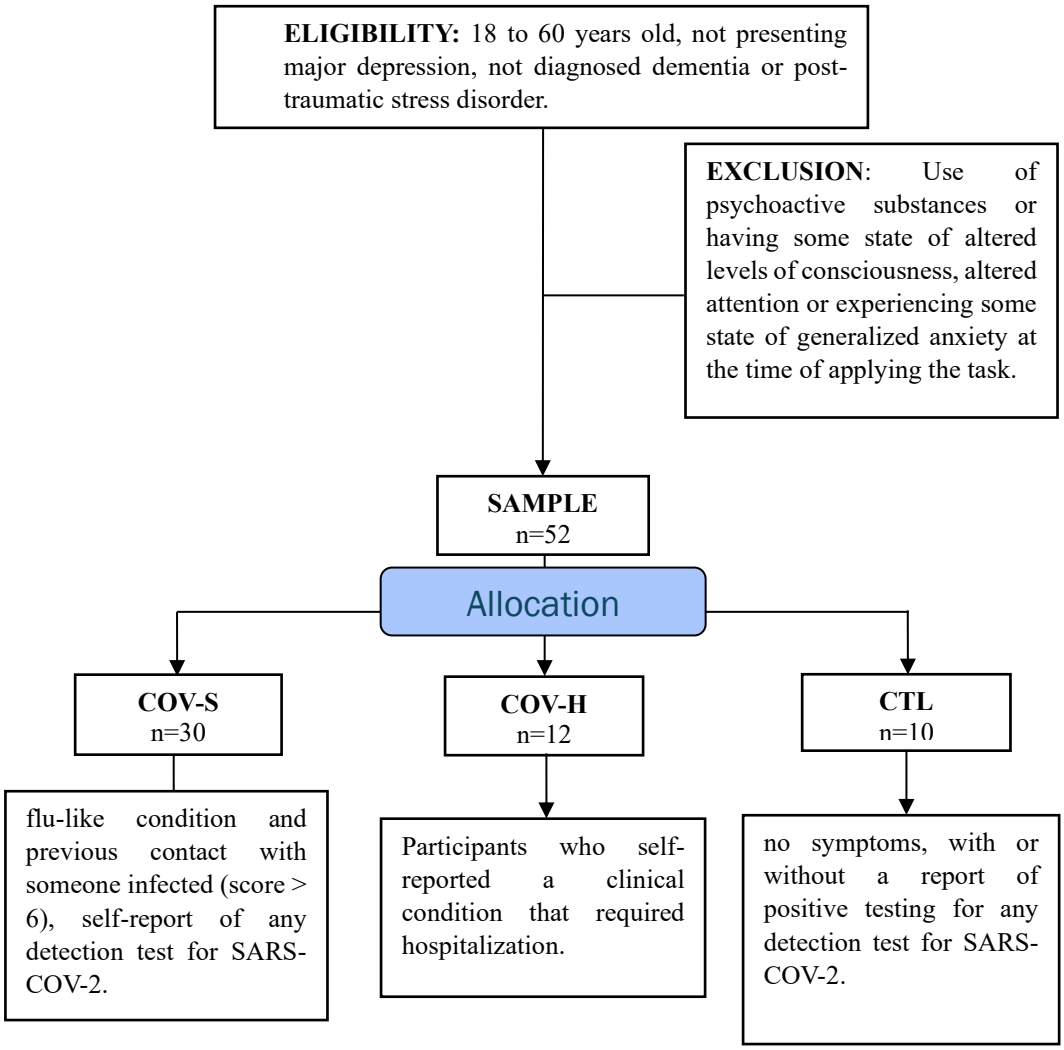

Figure 2: Flowchart of the study design, including the three groups (COV-S, COV-H, CTL), the calculations performed with G Power, and the evaluation criteria used in the neuropsychological tests.

ANEXO 2

QUESTIONÁRIO RASTREIO, SOCIODEMOGRÁFICO E CLÍNICO

Dados sociodemográficos

Participante nº
idade
gênero
uso de substância
escolaridade

QUESTIONÁRIO DE TRIAGEM (ADAPTADO da USP e Secretária de Saúde de São Paulo)

Você teve contato próximo com alguma pessoa testada positiva para COVID-19?

( ) Sim
( ) Não

Você já apresentou algum dos seguintes sintomas durante esse período de pandemia pelo COVID-19?

Febre: ( ) Sim ( ) Não
Calafrios: ( ) Sim ( ) Não
Falta de ar: ( ) Sim ( ) Não
Tosse: ( ) Sim ( ) Não
Dor de garganta: ( ) Sim ( ) Não
Dor de cabeça: ( ) Sim ( ) Não
Dor no corpo: ( ) Sim ( ) Não
Perda de olfato ou paladar: ( ) Sim ( ) Não
Diarréia (por motivo desconhecido): ( ) Sim ( ) Não

Você foi diagnosticado ou hospitalizado com a COVID-19?
( ) Sim
( ) Não

Você realizou algum exame de testagem para a COVID-19? Se sim, qual?

( ) Sim, kit de testagem rápida
( ) Sim, Teste sorológico
( ) Sim, RT-PCR (teste com swab nasal)
( ) Não, somente diagnóstico clínico
( ) Não realizei nenhum exame

Caso tenha realizado algum exame, qual foi a data da realização? DD/MM/AAAA

__/__/____

Histórico de condições clínicas prévia

Hipertensão ( )
Diabetes ( )
doenças cardíacas, qual:_____.
doenças respiratórias, qual:_____.
Doença oncológica, qual:_____.

Quadro clínico observado durante a infecção

Assintomático ( )
Sintomas gripais leve ou moderado ( )
Hospitalizado com condição controlada ( )
Hospitalizado com tratamento intensivo ( )
Quantos dias de internação: _____.
Período da infecção e tratamento _____.

Sintomas observados durante a infecção

Sintomas gripais
Febre Não:_____ Sim:_____
Tosse Não:_____ Sim:_____
dores abdominais Não:_____ Sim:_____
Fadiga Não:_____ Sim:_____

Sintomas neurológicos

Dores de cabeça durante fase aguda Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? _____teve ocorrência depois de curado?_____

Alteração na visão Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Redução auditiva Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Redução de paladar Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Redução do olfato Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Alteração na mobilidade Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Tremores Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Dormências nas extremidades Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Dores musculares - Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Perda de consciência Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Perda de memória - Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Alterações no sono - Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado?_____

Alterações na disposição? - Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado? _____

Alterações no humor - Não:_____ Sim:_____., teve ocorrência antes da infecção pela COVID? ____. teve ocorrência depois de curado? _____

Tipo de tratamento

Medicamentos antigripais ( )
Oxigênio terapia ( )
anti-viral terapia ( )
Interferon ( )
Antibióticos ( )
Corticóides ( )
outro ( ), qual:_____

ANEXO 3

UNIVERSIDADE FEDERAL DO SUL DA BAHIA - UFSB

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: ALTERAÇÕES DE PROCESSOS MNEMÔNICOS EM INDIVÍDUOS INFECTADOS PELO SARS-COV-2

Pesquisador: EZEQUIEL BATISTA DO NASCIMENTO

Área Temática:

Versão: 1

CAAE: 39223420.0.0000.8467

Instituição Proponente: UNIVERSIDADE FEDERAL DO SUL DA BAHIA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 4.368.891